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THE INFLUENCE OF THE PAST ON THE PRESENT AND FUTURE OF MEDICINE[1]

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Submitted for publication December 13, 1935

The progress of medicine is recorded in the history of mankind of the past twenty-five centuries. It is a record of struggle to win by toil the secrets of nature concerning man's body and its disturbances by disease and accident. Gradually, facts have gained general acceptance by verification. These facts have been classified and organized and concepts in harmony with these facts have been established regarding the structure, the function and the disturbances of the human body. Thus scientific medicine has been slowly and carefully built up, and today forms the foundation upon which stands the structure of medical practice.

The master builders who have shared in laying this foundation have had to toil not only to see and to understand in a new way the intricacies of life and death, but they have often had to contend with other men, less free than they, who were ruled by authority, tradition, speculation and mystical beliefs that they held as sacred. Medical progress has had to overcome prejudice, hatred, persecution and general indifference. For centuries the seeker of medical truth needed bravery and courage as well as a dominant will to know and to teach.

A brief review of the outstanding events of medical history presents the story of a series of great men, who learned from nature facts of fundamental importance and who cultivated new attitudes of thought and new methods of work. Leaving behind many fragments, the story may be begun with Hippocrates, the Father of Medicine, who lived in Greece from 460 to 370 B.C. He brought medicine down

[1]This paper was delivered as part of a lecture at the Peiping Union Medical College, Peiping, China, which was published in full in the Chinese Medical Journal, September, 1935.

from heaven to earth, and was the first physicain to study carefully the manifestations of disease by direct observation. He created too the lofty ethical standards of the doctor of medicine which have come down to the present day as the ideals of medical practice. Hippocrates set forth the idea that diseases were specific conditions of the body brought about by natural causes and which ran courses according to their characteristics. He founded the idea of diagnosis, but laid especial emphasis on prognosis, teaching man to predict the outcome of disease, and gave a rational basis for treatment which he conceived as assisting the natural powers of recovery. Hippocrates approached the patient directly and left outside of this relation the mystical and speculative ideas that had governed his predecessors. He stands today, somewhat dim in time but clear in the minds of men, as a genius of great character and wisdom, the most revered figure of medical history.

The Greek physicians continued to dominate the western world for six hundred years until Galen, who dying in about A.D. 200 left behind voluminous writings which were destined to rule medical thought and practice with an iron hand of authority all through the dark and middle ages, until the light of modern science dawned in Italy at the time of the great awakening—the Renaissance. Then the authority of the ancients, perverted and distorted by numerous transcriptions and translations, was shattered in spirit by Paracelsus, and overthrown by facts concerning the structure of the human body, by the young and intrepid Vesalius. He learned not from books but from the actual, careful study of his own dissections. Here, in 1543, modern medical knowledge takes its beginnings and direct observation of nature once more asserts itself as the only method by which facts can be established. Men with open eyes and open minds begin to apply themselves to the study of man.

At the turn of the seventeenth century a new interest began to fill the minds of the forward-looking inquisitive searchers for truth. They began to study nature by means of measurements. Galileo introduced exact measurements and applied the experimental methods to gain knowledge of the physical world. Sanctorius brought accurate measurement to bear on medical problems, initiated the study of metabolism, employed the thermometer to determine body tem-

perature and counted the pulse rate by means of the pendulum Galileo had demonstrated to him. The study of bodily functions with mathematical exactness set thought going in new directions, and in 1628, in England an epoch-making discovery was given to the world. In that year William Harvey published his great book "On the Motion of the Heart and Blood in Animals," and described for the first time in complete and irrefutable form the circulation of the blood. Here was the starting-point of a purely mechanical explanation of a vital phenomenon; here quantitative ideas were introduced into biology, here was the beginning of modern physiology and here the experimental method was used for the first time in the study of vital phenomena. A masterpiece of scientific writing was given to the world. A simple, thoughtful and independent man strove to wrest from nature one of her innermost secrets, and succeeded by great effort in doing so. William Harvey stands as a beacon light along the path of medical progress.

To complete the course the blood must travel in its circulation, finer structures than were revealed to the unaided eye are traversed, so that Harvey had to surmise that the blood flowed from the arteries and veins through minute vessels, the capillaries. A few years later, however, the microscope became available and in the hands of a man born in Italy in the same year in which Harvey published his account of the circulation of the blood, the capillaries were described by Marcello Malpighi.

In 1660 he showed the capillaries as a certainty which Harvey had indicated as a logical necessity. More than this, Malpighi, a man of the finest quality of mind and spirit, became the first great microscopic anatomist, and by his innumerable studies did much to reveal the finer structures of the human body. He is one of medicine's most attractive personalities, his character having been described as one of "sweetness and light."

During this seventeenth century important discoveries were made regarding the respiration, especially by the group of chemists led by Robert Boyle at Oxford and including Hooke, Lower and Mayow, who all but discovered the true nature of respiration and the identity of oxygen.

While medical science was being built on a firm foundation of well

established facts, the existing concepts of disease and of its treatment were being undermined. Old theories and ideas no longer sufficed to satisfy the students of disease, as the new knowledge was distinctly disturbing to the old conceptions. New theories had to be propounded, and speculations regarding the control of the body and its disturbances resulting in disease became the order of the day. The medical ideas of the seventeenth century became a seething mass of generalizations, which grouped themselves about two dominant ideas. One held that the body was a mere mechanical device operating each of its parts like machines or tools. This school was known as the iatrophysicists. The other central idea was that chemical forces controlled the activities of the body and its various organs, and about it was formed the school of iatrochemists. Between them the poor patients of the day could hope for little clear thinking or real understanding of their maladies.

Upon this scene of chaos strode a gallant fighting man Thomas Sydenham who knew nothing of these speculations, nor did he know of Galen, Vesalius or Harvey. He did know, however, of Hippocrates, of Francis Bacon, of Cicero and of Don Quixote, and best of all, he was a man of action possessed of piety, common sense and good humor. In his life extending from 1624 to 1689, this English physician re-established the broken connections between the best of ancient medical practice and that of modern times. Sydenham returned again to take up the work of Hippocrates, to study disease by direct observation of the patient, keeping the speculations and the theories of his age from coming between him and the object of his study—the sick man. Sydenham differentiated diseases, and set the medical world on the road it has continued to follow, the road leading to the diagnosis of disease, its differentiation into specific entities and a plan of treatment best suited for each disease.

The acceptance and spread of the knowledge and methods of Sydenham had to await a great teacher who believed in him and his methods, and such a one did not appear for fifty years, until Herman Boerhaave, of Leyden, spread the gospel of Sydenham to the four quarters of the western world, whence came his students to Holland. Boerhaave taught medicine at the bed-side, and brought great learning, charm and personality to his task, so that his disciples went

forth to found other great centers of medical education in Vienna, Edinburgh and elsewhere, and the ideas of Sydenham became the foundation upon which the modern structure of medical practice began to be erected in the early years of the 18th century. The doctor of this time had learned much of the manifestations of disease as revealed by the study of symptoms and by the direct observation of the patient, but he knew little of what was going on within the body at the seat of disease. Much knowledge had accumulated about the gross and microscopic structure of the body and many new facts had been learned regarding its functions, physiology having been especially advanced and correlated by the stupendous industry of the Swiss physician Albrecht von Haller.

The year 1761 brought two new lights to brighten the road along which the forces of medical science were now advancing. In that year Giovanni Morgagni published his great work "On the Seat and Causes of Disease, investigated by anatomical methods," which marks the beginning of modern pathology, and Leopold Auenbrugger gave to the world his little book on percussion of the chest, extending the method of the study of the patient so that from now on he was to be examined as well as observed. These two important contributions, one from old Padua and the other from the newly established school of Vienna, were doubly important because they brought together the means of establishing anatomical diagnosis. But again fifty years were to pass before these new methods were to be fully understood and practiced. They were, however, fully appreciated and further developed in the great school of Paris, under the stimulus of the influential Corvisart who became the physician of Napoleon Bonaparte. Here, too, the grave, thoughtful and industrious Laennec invented the stethoscope and revealed many new facts regarding the diseases of the chest, especially pulmonary tuberculosis, of which he was a victim at an early age.

Again a great teacher comes forward to spread the new knowledge to distant lands, and Pierre Louis in the middle of the 19th century attracted many a student from England, Ireland, Germany and now America, sending them back to carry forward with great activity the diagnosis and differentiation of disease. With the work of Skoda and Rokitansky in the revived school of Vienna physical diagnosis

and pathological anatomy reached new developments of exactness, order and objectivity. The concepts of disease based upon the anatomical changes in the various organs of the body unfortunately failed to contain much promise for the treatment of disease. It swept away the theories and formulas upon which therapeutics had been based, but gave very little in its place.

The world of suffering man needed new ideas upon which the cure or relief of disease could be grounded and the school of physiological medicine, arising and developing about the wonderful German Universities, gave hope in this direction. Towards the end of the first quarter of the nineteenth century Johannes Müller, physiologist, anatomist and pathologist attracted to his school, first at Bonn and then at Berlin, a group of students such as the modern world of medicine had not seen before. From the laboratories of Müller went a veritable crowd of men who were destined to lead medicine into the great new field of scientific research, in which all sciences and all methods of research were to be industriously and systematically applied to the deeper study of medical problems. Led by Rudolph Virchow, this group did much to give a new direction to medicine and to accelerate the speed of medical progress. Virchow, in 1856, published his epoch-making treatise on cellular pathology and brought the study of disease down to the ultimate structural unit of the body,—the cell. He and his followers constantly emphasized the idea that the disturbances of function constituted the true basis of disease and utilized extensively animal experimentation to throw new light on the problems of disease in man.

Although the German school had an absorbing interest in the pursuit of laboratory studies which drew attention away from the direct study and treatment of patients, a new attitude became apparent in about 1870. At this time, initiated by the invention of the stomach pump by Kussmaul in 1867, German medicine showed an awakened interest in the investigation of disease in patients, and inaugurated the era of functional diagnosis. The teachings of pathological physiology came to have direct application and patients began to be intensively studied from the point of view of functional disturbances. These studies, which have steadily progressed from that time to the present, introduced a multitude of chemical and physical

methods into hospital and clinic, and not only added greatly to the details of knowledge regarding disease, but also gave many new lines of approach for its treatment. These new methods of study also raised a hope, heralded especially by Rosenbach, that disturbances of function could be recognized before actual pathological lesions had become well established. Although this hope proved for the most part vain, it did focus attention on the earliest manifestations of disease and added much to the conceptions of its treatment. Functional disturbances of the gastro-intestinal tract, of the heart and circulation, of respiration and of the kidneys, have furnished a very fruitful field for study by a veritable army of investigators, which is still going forward. New lines of work have been discovered, especially in the fields of the endocrine glands and in dietetics. The hormones and the vitamins have come recently to stand out prominently among the new objectives of attack.

While pathological anatomy and physical examination of patients had become accepted as the backbone of the diagnosis of disease, and while pathological physiology was being developed as a means of explaining many of the phenomena of disease and disclosing new methods of treatment, a new country of wide expanse composed of several fields had been discovered and was rapidly being cultivated. A French chemist of great vision, industry and skill had been drawn almost by accident into the fields of medical science. Louis Pasteur appeared, to make his name immortal by giving convincing and dramatic demonstrations of the rôle that micro-organisms play in the causation of disease. Following other important work such as his studies on fermentation and on *pébrine*, a disease of silk-worms, in 1877 Pasteur announced his astounding discoveries of the bacterial cause of chicken cholera and of anthrax, and soon demonstrated by experiments of boldness and decision the production of active immunity by the injection of attenuated micro-organisms into animals. This was followed by one of the most dramatic events in the annals of medicine—the successful prevention of hydrophobia in those who had been bitten by mad dogs, following the successful cure of Joseph Meister, the Alsatian boy, in 1885.

Robert Koch was the next great figure in this new field of bacteriology, and he made many important contributions. Koch demon-

strated the microbic origin of certain diseases, developed widely the technique of bacteriology, devised methods of sterilization and as the crowning glory of his work discovered in 1882 the cause of tuberculosis—the tubercle bacillus.

Following these two great leaders, who were the first to take possession for medical science of this newly found country of bacteriology, came many splendid workers who discovered the specific causes of old diseases and found new organisms which were the incitors of diseases previously not recognized as specific entities. New light was thrown on the transmission of disease, new methods of treatment were devised, much illness was prevented and many lives were saved. A great pioneer in the application of this new knowledge was Joseph Lister, the British surgeon. Born in 1827, he was a contemporary of Pasteur, with whom he collaborated. In fact Lister began the study of wound infection before the advent of systematic bacteriology, and his early work, based on conjecture rather than on demonstrated facts, received but scant recognition, in spite of the favorable clinical results that he demonstrated. His introduction of antiseptic surgery, however, prepared the ground for the epoch-making developments of modern aseptic surgery, of which Lord Lister was eventually proclaimed the originator. His work and that of his illustrious followers, coupled with the great boon to mankind, the discovery of ether and chloroform as general anesthetics, made possible the enormous expansion of surgery, with many technical improvements and extensive widening of knowledge through surgical pathology. It opened also many new avenues of study of disease derived from the use of animal experimentation.

Having learned much regarding the transmission of disease through bacteriological research, man now stands in a new position in his relation to nature. He is armed as never before to guard himself against the innumerable noxious agents ready to invade his state of wellbeing or to capture even his life. Not only is knowledge available by which many acute infectious diseases can be repelled, but much has been learned about the natural forces of the body which are constantly protecting it against invasion by disease. Scientific study is progressing rapidly in two main directions, one aiming at the removal from human society of all forms of disease-producing germs, the other,

known as Hygiene, aiming to build up the resistance of man to disease by perfecting the conditions of life and modes of living. Public Health and Hygiene now go forward as the great new force for the betterment of man's existence on earth. Here at last man seems to have reached the ultimate objective in his struggle with the forces of nature that menace his physical wellbeing and cut short the natural span of his earthly existence.

In this brief review of the development of modern medical science, and of some of the distinguished men who spent their lives for the benefit of mankind, it is impressive to think of the many different types of human endeavor and the numerous leaders of thought in various countries who have joined in this steady march of progress since the Renaissance. Today medical science is extensive in scope and deep in significance. It is now divided among a number of disciplines which have been elevated to high standards of learning and to serious consideration by the great Universities of the world. It is being constantly expanded by the contributions of scientists in all parts of the world, not only by those working in the more restricted fields of medical research, but also by those engaged in the study of almost every field of the natural sciences.

The outstanding center of medical learning has never remained for very long in any one country or city. The birth-place of modern medicine is found in the old city of Northern Italy, Padua, where under the patronage of the free and rich republic of Venice the modern spirit of medicine grew up and spread afar its early influence. Then, in the eighteenth century the center of medicine was found to have crossed the Alps to Holland, and Leyden claims the distinction of being the city which led the world in medicine. At the beginning of the nineteenth century Paris held the center of the stage until toward the middle of the century the Teutonic peoples, awakening from their dreams of natural philosophy, brought the center of medicine first to Vienna and then, by the application of the modern spirit of research, to Berlin and other great German universities.

England, Scotland and Ireland brought forth not only contributions to medicine of the highest order, but perhaps surpassed all other lands in the development of the medicine of the bedside without ever attaining the same enthusiasm for continued research in the more

fundamental problems of disease that has been seen in other countries. Here, however, clinical teaching, with the patient as the center of study, was developed to the highest point, the spirit of Sydenham having been retained as a national heritage.

The spirit of English medicine was that from which America drew her early inspiration, the school of Edinburgh being an especially potent influence in the medical practice and teaching of the United States in the years following her independence from England. In the eventual course of events, however, when America became of age and took her place among the nations, with a medical self-consciousness, and began to make her own contributions to medical progress and science, it was largely the happy combination of the traditions of the British school and the spirit of research of German origin that exerted the greatest influence. As the recent developments of medical science in the United States have had such a deep influence on the introduction of western medicine in China, it seems possible to trace the progress of modern medicine through America to our very doorstep.

In 1884, an event took place which was to prove of signal importance, not only to American medicine but in the course of time to the medicine of China as well. In that year a talented young man, fresh from the best laboratories of the German Universities where he had worked for several years with some of the leaders in medical research, was appointed professor of pathology in the Johns Hopkins University at Baltimore. This young man was William H. Welch. The University had at that time no medical school, but had set for itself high University standards and was inaugurating for the first time in America true graduate studies, based upon the model of the German Universities, in which scientific research was the life-blood. A splendid great hospital was in the process of construction closely affiliated with the University, both having been generously endowed by the same benefactor, Johns Hopkins, a merchant of Baltimore. The plans of the University called for the establishment of a medical school as soon as it could be provided for, and Dr. Welch was called to Baltimore with the idea that he should eventually organize a medical school in conjunction with the Johns Hopkins Hospital, and establish medical education on the same high academic level that was

being maintained in the University as a whole. He succeeded in gathering about him the most highly trained and talented group of men that had ever been brought together in America, and in 1893 the Johns Hopkins Medical School was opened. Its requirements for admission were far in advance of those in force in any other American school; its spirit was that of a true University, and scientific research of a high order was demanded of all members of the teaching staff. A new note was sounded in American medical education, which was destined to resound throughout the nation. Many of the initial plans of the Johns Hopkins Medical School were considered by those directing its destinies as experimental, but so well were they founded, with such wide vision and wisdom, that they have not only been maintained to the present time, but have largely been incorporated consciously or unconsciously throughout the educational system of the United States.

During its early years the Johns Hopkins Medical School met much opposition from without. The medical profession claimed that it was not in harmony with the needs of the country, that its graduates had poor training in the practice of medicine, that the school was turning out research workers and not doctors, that the graduates had a conceit which made them undesirable staff members and supercilious critics. Much of this was true when viewed with the narrow vision of those whose medical knowledge and methods of practice were neither scientific nor based on sound training. As years rolled by, however, the graduates of the Johns Hopkins school became leaders not only in research and in teaching, but also in medical practice in all parts of the United States.

Dr. Welch had been the leading spirit in American medicine for nearly fifty years, up to the time of his death in 1934, and his contributions to the organization of medical education, to the direction of research, to the training of men, to the development of public health and hygiene and to his leadership in the study of medical history rightfully accord him a place as one of the greatest men of medicine in modern times. He was for years one of the chief advisors regarding the development and support of medical education and research through the funds which Mr. John D. Rockefeller has put at the disposition of those competent to direct the expenditures for the advancement of medicine.

Among the brilliant group of men called to form the initial faculty of the Johns Hopkins Medical School was William Osler, who was appointed professor of medicine. Born in Canada in 1849, he was an ever youthful and charming spirit until the day of his death in 1919. It was he who brought the spirit of English bedside medicine to flourish side by side with the spirit of German research so well represented by Welch. Osler and Welch formed a great combination, such as have been seen in Skoda and Rokitansky, Schönlein and Johannes Müller, Traube and Virchow, combinations representing the best of medical practice and of medical science. Osler considered his introduction of the students into the wards of the Johns Hopkins Hospital, as part of the professional organization of the medical service, his greatest contribution as a teacher. It is quite natural that he should have taken special pride in this important forward step in the educational procedures of his time, for no man of modern times has given and received from his students truer affection, devotion and companionship. He reached the high distinction of being the greatest physician of his time. A man of unusual charm, good humor and sympathy, he was talented as a writer, learned as a scholar, a genius in social grace. While in Baltimore, although heavily burdened by the many duties of the hospital and of private practice, called upon for innumerable addresses, which he delighted to make, and a strenuous worker in the library and in the clinic, he gave up one evening a week throughout the entire academic year to a small group of students. They, the clinical clerks on the medical wards, would assemble each Saturday night at his house to listen to his talk on medical history and would then discuss the interesting clinical problems that had been encountered during the week. Osler was not a great contributor to medical science, but he was one of those great teachers like Boerhaave at Leyden and Louis at Paris, who organized medical knowledge, taught with rare skill, enthusiasm and charm, and sent forth true disciples of Hippocrates to many parts of the world to give their best in the cause of medicine.

One of Osler's greatest accomplishments, again for the sake of his students, was to write a textbook of medicine which was perhaps the best in any language for many years from 1892, when the first edition appeared. This textbook fell into the hands of Mr. Gates,

the chief advisor of John D. Rockefeller at the time when this unprecedented philanthropist was ready to turn from the acquisition of wealth to the large and serious task of its distribution. Osler's textbook made such a deep impression on Mr. Gates regarding the value of modern medicine and its worthiness of support, that he was largely instrumental in having the support of medical education and medical research as a major function of the enormous foundations established by Mr. Rockefeller.

The art of medicine has been defined as the application of the science of medicine to the needs of the individual patient. In reviewing the contributions which have been the milestones of medical progress, one cannot but be impressed with the vast amount of scientific knowledge now available for application to the individual patient. The method of our forefathers, or perhaps of our fathers and mothers was to have one physician, known as the family doctor whose duty and privilege it was to apply the teachings, the techniques and the principles of medical science to the individual patient. A large share of medical practice, and certainly the initial responsibilities were therefore in the hands of the general practitioner. As the scope of medicine increased, specialism spread. As new technical methods of diagnosis and treatment developed, special training was needed for their proper application. Today thorough knowledge is possible in only a small division of medical practice. A serious illness may require the services of a dozen persons; physicians, surgeons, specialists, laboratory workers, x-ray experts, nurses, dietitians and many more to bring the best of medical science to bear upon the problems of the diagnosis and treatment of the patient.

An arresting question for society today regarding medical service is: How is it possible for the ordinary person to pay the costs of a modern medical care of serious illness? The question is perplexing the people and the medical profession of all countries, except perhaps those of Russia. The medical profession of the United States is in a quandary, and the leaders of organized medicine are searching for a solution of the problems presented by the costs of medical care. The private practice of medicine as a means of furnishing medical care to the people as a whole, seems to have broken down under the weight of medical science. Medical knowledge has been divided

into many specialties, and the man in trouble often does not know which way to turn.

It has been suggested that medical education should supply the means of answering this question and that a simplified form of medical practice should be taught. Medical educators, however, have not found a way to eliminate from the educational program important facts which constitute the scientific basis for the understanding of disease and for the treatment of the patient. Medical educators are not willing to accept the responsibility of teaching a system of practice which does not put into the hands of the physician knowledge which he may need in order to save human life.

Other plans of relief have been suggested, and all that hold real promise seem to contain a fundamental change in the status of the doctor and in the relation of doctor to patient. There is much to commend the principle, however, that the costs of medical care must be proportioned among all the people, and paid for during times of good health and maximum productivity, and that compulsory health insurance conducted by the state and applicable to all the people, may be the ultimate solution. This problem of medical service is largely caused by the accelerated growth of medical knowledge, the outcome of medical progress, and is before the world for future solution.

There remains one more lesson of medical history to be considered, one more question to be raised. The development of public health and hygiene has given to man the means of preventing many of the diseases which attack him, and of developing his state of living so that he will be less prone to illness than in the past. Should this be considered as the last objective of medical practice? If the ultimate aim of medicine is to protect man, perhaps it need attempt to go no further. But man is harassed not only from without. He has a mind, a spirit, as well as a body. Little attention has been given to the suffering of man through his emotions. Many people who have no apparent medical disease are yet far from well. Here lie the problems of the future. An improvement in human happiness should be the next great objective to which the best minds of medicine may be applied. The human mind must be better understood, and must be the subject of more serious study and research from the medical

viewpoint. It is known vaguely how largely the mental state may be responsible not only for generating discomfort and suffering, but also for the actual production of organic disease. The time has come to convert these beliefs or surmises into scientific facts. Some progress has already been made in the field of mental hygiene, but much greater progress can be attained with a broad approach through medical sociology.

The doctor may do much to improve the happiness of man not only by taking part in carrying out broad projects of social adjustment but also by acquiring a deeper knowledge and understanding of the human emotions, mental problems and social difficulties of each individual to whom he renders service. Let the medicine of the future carry along all that is essential and valuable that has been learned in the past by those who have lived in past generations. Let medicine do all it can to prevent disease and improve the state of hygiene, but let it not stop here. The doctors of the future should have at their disposal more knowledge for the increase of human happiness, and may the generation now coming on and those to follow give to this problem their best minds in the same spirit of unselfish toil that distinguishes the leaders of medical progress in the past.

CLINICAL OBSERVATIONS UPON THE IMPORTANCE OF THE VESTIBULAR REFLEXES IN OCULAR MOVEMENTS

The Effects of Section of One or Both Vestibular Nerves

FRANK R. FORD and FRANK B. WALSH

From the Johns Hopkins Hospital Neurological Clinic and Wilmer Ophthalmological Institute, and the Medical Service of the Baltimore City Hospital

Submitted for publication January 20, 1936

Since the introduction of the Bárány tests many years ago, it has been well known that nystagmus, vertigo, and other symptoms might be produced with ease in all normal subjects by stimulation of the vestibular apparatus. The physiological significance of the vestibular reflexes has not been entirely clear, however, and several observers have concluded that they serve no useful purpose. Hobhouse (1) states, "In the semicircular canals man possesses a beautiful and complex mechanism which has been superseded by higher development, and whose only positive function now is to produce some of the most disabling and distressing symptoms which the human body can experience."

The writers believe that the following observations are of considerable interest in that they illustrate the physiological value of the vestibulo-ocular reflexes in ocular fixation, and demonstrate the symptoms which arise when these reflexes are abolished.

We wish to thank Dr. Boggs, Dr. Dandy (3) and Dr. Meyer for permission to report the following cases:

Case history 1. (J-52789) *Man of 47 years developed progressive paralysis of all ocular movements beginning with loss of upward movements, then loss of downward movements and, finally, loss of lateral gaze to either side. No diplopia, loss of vision or alteration of pupillary reflexes. Strong and persistent deviation of the eyes on vestibular stimulation but no nystagmus. By means of slow active and passive movements of the head during ocular fixation, the eyes might be moved in all planes. Progressive course ending in bulbar palsy, pneumonia and death. Postmortem exam-*

ination: Degenerative process involving the cortex of the brain, the lenticular nuclei, and descending fiber tracts in the brain-stem.

S. S., a man of 47 years, previously healthy, noticed that he could not rotate his eyes upward in January 1930. Shortly after this he found it difficult to rotate them downward. There was no difficulty in opening or closing the eyes and no diplopia. At night he had frequent clonic movements of the muscles about the left jaw. Sleep was disturbed. There was sexual impotence. The symptoms slowly increased so that by the spring of the year he was unable to move the eyes in the vertical plane at all. On July 17, 1930, he came to the Out-patient Department.

Neurological examination revealed only a complete loss of upward and downward associated movements of the eyes. The lateral movements were of full range. There was no ptosis and no diplopia. The pupils were equal, circular, and reacted to light and during accommodation. The ocular fundi appeared normal. Vision was good. Visual fields were full. General examination was essentially negative. The spinal fluid contained no excess of cells. The globulin reaction was negative, the mastic curve flat, and the Wassermann reaction negative. Roentgenographic studies of the cranium, the sella and the orbits appeared quite normal. Ophthalmological examination did not add to the findings of the neurological study.

The patient did not improve and lateral movements of the eyes became limited. He entered the Henry Phipps Psychiatric Institute on October 2, 1930.

There was complete loss of lateral, as well as of upward and downward movements of the eyes. They were fixed in the central position. From time to time there were clonic spasms of convergence during which the right eye moved inward more than the left. The spasms of convergence were synchronous with clonic movements of the left side of the face and left jaw. These movements were not constant but at times occurred rhythmically at a rate of about one per second. The pupils remained equal, circular, and reacted normally to light. The corneae had become hazy, resulting in diminished visual acuity. Slit-lamp examination of the corneae revealed superficially situated minute vesicles filled with clear fluid and circumscribed grayish-white patches in the deeper layers. The corneal reflexes were diminished. The corneal lesions were believed to be due to neurotrophic keratitis. There were no changes observed in the optic fundi.

When the patient was instructed to fix an object with his eyes and his head was then rotated, the eyes tended to move so as to maintain fixation. In this manner upward movements of about 15 degrees were obtained, as were downward movements of small amplitude, but lateral movements to both right and left were of full range. When the right ear was irrigated with cold water, strong tonic deviation to the right occurred and persisted for more than three minutes after the irrigation was discontinued. A similar deviation to the left was obtained when the left ear was irrigated. Rotation of the patient in a Bárány chair produced the same results, *i.e.*, there was no nystagmus but a strong and persistent tonic

deviation of the eyes occurred in the direction of the slow phase of normal nystagmus.

The patient's condition steadily grew worse. Vision became greatly impaired, bulbar palsy developed and finally, some 10 months after the onset of his symptoms, he died of pneumonia. Postmortem examination revealed degenerative changes widely scattered throughout the brain. The cortex and lenticular nuclei were atrophic and there were extensive degenerations in the corticobulbar tracts, posterior longitudinal bundle, and other descending tracts in the brain-stem. The nuclei of the cranial nerves were not directly affected. The histological changes were suggestive of epidemic encephalitis.

Case history 2. Complete left hemiplegia due to embolism. Conjugate deviation of the eyes to the right with paralysis of left lateral gaze. Tonic deviation of the eyes but no nystagmus on irrigation of the right ear. Passive rotation of the head to the right during ocular fixation caused full left lateral deviation.

C. W., man of 43 years, was shot through the left lung on July 15, 1935. There was hemorrhage into the pleural cavity and severe shock. For a week or more there was moderate fever. The patient then began to improve rapidly and was almost ready to be discharged when, on July 29, he was found in a semi-stuporous condition with complete left hemiplegia. The next day his mental condition was much better but there was no change in the paralysis.

Examination on the third day of the paralysis revealed that the patient was quite rational and cooperative although he was rather slow to grasp what was expected of him. The eyes were strongly deviated to the right and could not be moved more than a few degrees toward the left, never reaching the midline. They could be moved upward and downward fairly well and might also be carried into the extreme right lateral position. The movements were the same whether the eyes fixed a moving test object or were moved voluntarily as requested. When the patient was told to fix the eyes upon some object within the field of vision and the head was then passively rotated to the right, the eyes moved into the extreme left lateral position. There was no squint, no diplopia, and no nystagmus. The pupils were circular and equal and reacted normally to light and during accommodation. Vision was normal. There was complete left homonymous hemianopia. The optic fundi were normal.

The left arm was completely paralyzed and very flaccid, though not completely devoid of tone. The left leg could be moved slightly, especially in flexion at hip and knee, and showed more tone than the arm. A moderate degree of weakness was present in the muscles about the left side of the mouth. Sensibility was much reduced over the whole left side. There was complete loss of sense of passive movement of the fingers and toes, of sense of posture and of tactile localization. There was also some reduction in the appreciation of touch, pain, and thermal stimuli. The tendon reflexes were still somewhat diminished on the left side, and there was a typical Babinski reflex on plantar stimulation.

The ears were irrigated with cold water. On the left this produced normal

nystagmus, *i.e.*, there was a slow movement to the left with a quick compensatory movement back toward the midline. The eyes were moved well to the left of the midline, almost into the extreme left lateral position during this stimulation. When the right ear was irrigated, the eyes were rotated more strongly than ever to the right, but there was no quick movement to the left and, hence, no nystagmus.

When the patient was seen again three days later, the deviation of the eyes had disappeared and voluntary movements of the eyes were of full range. Within a few weeks he was able to walk, despite the presence of a severe left hemiplegia with spasticity. Three months later he showed no further improvement.

The reactions elicited in the two cases abstracted above are, of course, well known (4). They are presented for comparison with the four cases which follow.

Case history 3. (J-85835) *Man of 43 years developed paroxysms of vertigo with mild reduction of hearing and some tinnitus. Operative section of the vestibular components of both eighth nerves with complete relief of original symptoms. Post-operative development of unsteadiness on turning head and uncertainty when crossing street. Loss of ocular fixation during movements of the head. No change in hearing, but complete loss of all vestibular reflexes.*

J. B., a man of 43 years, developed paroxysms of vertigo which were often accompanied by vomiting and which sometimes lasted a day or more. There was slight tinnitus aurium on either side and mild reduction of hearing in both ears, more especially on the left. The vestibular reflexes were normal. Neurological and medical examinations revealed nothing of importance except for mild hypertension. The Wassermann test was negative. A diagnosis of paroxysmal aural vertigo, or Ménière's syndrome, was made. The patient was treated by various conservative methods without result.

Because the attacks continued and became more severe, Dr. Dandy performed a craniotomy and severed the vestibular component of both eighth nerves. This put a stop to the paroxysms of vertigo and resulted in complete loss of all vestibular reactions on turning and irrigation of the ears. The audiometer chart showed no change in hearing following the operation.

During convalescence it became evident that a new series of symptoms had developed. Objects seemed to move before his eyes unless his head was kept perfectly still. Walking caused objects to "jump" before his eyes to some extent, but this did not interfere much with his gait. He found, however, that when crossing the street, he was apt to be very unsteady because he would have to turn his head to either side to look for approaching cars. Consequently, he had become accustomed to hold his head very stiffly and to walk in straight lines looking directly before him. He was also very unsteady in the dark.

Examination eleven months after the operation revealed normal vision and normal pupillary reactions. The optic fundi showed no pathological alterations. There was no squint and no ptosis of the lids. The ocular movements were of full range in all planes. Hearing was good except for a slight reduction of the high tones in either ear, which had been present before operation. There was

no weakness, spasticity, or incoördination in the extremities. In brief, except for the evidences of loss of vestibular function, the neurological examination was quite negative. The station was quite steady when the eyes were open, but when they were closed the patient swayed a little, although he was never in danger of falling. The gait was normal when he was permitted to walk in a straight line. It was noted that he first fixed an object with his eyes and that he held his head very stiffly. When his eyes were closed, his gait became unsteady. If he was required to turn his head from side to side as he walked, he became very unsteady and staggered. The patient stated that when he was walking, objects seemed to "jump" before his eyes. When he was requested to walk with long steps, the "jumping" increased and, when he was pushed in a wheel chair over a smooth floor, this symptom disappeared. It seemed probable that the "jumping" of objects was due to bobbing up and down of the head which always occurs to a certain extent in walking, and which is increased when long steps are taken. When the patient was seated, movements of the head caused objects to "jump" before his eyes. During this test, the examiner could observe irregular synchronous movements of the eyes of small amplitude which were predominantly horizontal. When the head was fixed so movement was impossible, ocular movements were normal and no nystagmus was observed. When the patient was asked to fix a revolving drum, marked by vertical stripes, normal ocular nystagmus was induced in all planes.

Some fourteen months after the operation, reëxamination revealed no further change in the patient's condition.

Case history 4. (U-65874) *Progressive deafness in both ears. Violent paroxysms of vertigo at the age of 38 years. Section of both vestibular nerves. Relief of vertigo and loss of vestibular reflexes. Impaired ocular fixation during movement of head.*

P. B., a man of 48 years, complained of ringing in his ears and of progressive loss of hearing of many years' duration. For about nine years he had been troubled with sudden attacks of vertigo and vomiting. During such attacks he was unable to stand or even lift his head. After an hour or more he would feel as well as ever. These attacks slowly had grown more frequent and more severe. No other symptoms could be elicited. The patient had never had otitis.

Examination revealed a well developed and well nourished man of middle age. There was bilateral deafness which was most severe in the higher tones, but also involved the middle range. Irrigation and rotation revealed that the vestibular reflexes were active on both sides. Otological examination revealed no signs of middle ear disease. Neurological examination was negative. The Wassermann reaction was negative. Blood pressure 130/85. On November 6, 1935, Dr. Dandy cut the vestibular component of both eighth nerves. Hearing was not reduced in the left ear, but some increase in the deafness resulted in the right ear. The vestibular reflexes were abolished, and the paroxysms of vertigo ceased.

Examination on the tenth day after operation revealed the same signs and symp-

toms described in the preceding case. When the patient was lying in bed and his head was still, his vision was clear and he was conscious of no vertigo. There was no nystagmus. When the patient attempted to stand or walk he was unsteady, but could walk without support. He was an ignorant man and found it difficult to describe his sensations. Objects, he stated, seemed to "shiver" before his eyes when his head was moving. When he was requested to follow a test object which was moved about before him, there were fine irregular movements of the eyes. These were due to the slight movements of the head, for when his head was fixed, they ceased and his vision became clear again. If he turned his head when walking, he became so unsteady that he would fall unless supported.

Case history 5. (U-1418) *Chronic otitis media with deafness in childhood. At age of 38 years, attacks of sudden vertigo. Operative section of right VIII nerve. Relief of vertigo, but impairment of ocular fixation on movements of head, especially to the right.*

C. D., a woman of 38 years, entered the hospital in June 1935. She stated that she had been deaf in the right ear since early childhood after developing an acute otitis media. There had been an intermittent discharge from the ear ever since. All her life, the patient had been subject to vertigo whenever she rode in a train or automobile, and she was made sea-sick by the least roll of a boat. In March 1935, she had had a sudden violent attack of vertigo with nausea, tinnitus and unsteadiness of gait which lasted several hours. After this she noticed numerous mild attacks of the same nature. These diminished in intensity and in frequency until June 7th, when she had another violent attack which rendered her unable to stand for a time.

Examination revealed chronic otitis media on the right with some discharge. There was more than fifty per cent loss of hearing and some reduction of vestibular reactions. Complete medical and laboratory investigations revealed nothing else of importance.

On June 15th Dr. Dandy sectioned the right eighth nerve. In the next few days there was the usual postoperative reaction. There was intense vertigo and nystagmus. The nystagmus was increased by deviation to the left and the slow phase was always toward the right side. When the patient got out of bed, she showed a tendency to fall to the right. Any movement of the head caused a great increase in the vertigo. These symptoms slowly receded and after several months the patient regarded herself as quite well. Needless to say, there were no further attacks of paroxysmal vertigo.

On September 10, 1935, the patient was examined again. She could walk and stand quite steadily when the eyes were open. When the eyes were closed, she would stagger to the right. The same difficulty, of course, developed when she tried to walk in the dark. Any oscillation of the head, such as that produced by walking down the steps or over rough ground, caused objects to oscillate before her eyes. This did not occur when walking on smooth surfaces. Sudden turning of the head brought on the same symptom and would sometimes cause staggering.

This reaction was definitely greater when the patient turned her head to the right. Slow movements of the head were ineffective in this respect. If the patient's eyes were carefully observed when her head was sharply turned to the right, a brief oscillation of the eyes was apparent. So long as the head was fixed, there was no nystagmus whatever, no matter what ocular movements were carried out. The right ear was, of course, quite deaf and vestibular stimulation revealed no reaction. All reactions of the left ear were normal.

Case history 6. (U-47262) *Progressive deafness and tinnitus in the right ear noted at the age of 14 years. Paroxysms of vertigo beginning at the age of 26 years. Operative section of right eighth nerve. Relief of the vertigo, but apparent oscillation of objects whenever the head was in motion for the first 3 months after operation. Complete recovery.*

C. L. R., a young physician entered the hospital on January 24, 1933, because of paroxysms of vertigo associated with vomiting and inability to stand. These had been present for several months and occurred at intervals of about two weeks. Since the age of 14 years, the patient had been troubled by tinnitus in the right ear and he was conscious that hearing was slowly failing in that ear. There had never been any otitis. The past history was negative except for tuberculosis of the epididymis with operation at the age of 20 years and symptoms of renal tuberculosis at the age of 23 years. The tuberculous infection had been inactive for more than a year when the patient entered the hospital.

Examination revealed a young man in good general physical condition. Hearing was much reduced in the right ear, most severely in the lower and middle range. The vestibular reactions of the right ear were less active than those of the left ear. The right ear drum was somewhat retracted but not scarred and the Eustachian tube was inflated with ease. Nothing else of significance was found. The Wassermann reaction was negative. The right eighth nerve was severed by Dr. Dandy a few days later. Complete deafness and loss of vestibular reactions in that ear resulted. The paroxysms of vertigo were relieved at once.

For several weeks the patient could scarcely walk without support because of loss of equilibrium and because of apparent jumping and oscillation of objects before his eyes. When his head was immobilized, his vision was clear and there was no apparent movement of objects, but the least movement of the head made everything seem to move before him. Turning of the head to the right caused this phenomenon to appear in a more severe form than turning to the left. Several weeks later the patient could walk steadily if he was careful to avoid sudden movements of the head, but even then he found that his powers of ocular fixation were so deficient that he could not always recognize friends whom he passed in the hospital corridors, since their faces appeared to be in constant violent motion. If he would pause a moment and hold his head still, he could see clearly. The patient found that riding in an automobile caused the same phenomenon unless the road was quite smooth for the least bouncing of the car made objects dance before his eyes. These symptoms slowly diminished and the patient ceased to notice them about three months after the operation.

Examination in November 1935, almost three years after the operation, revealed no difficulty in ocular fixation whatever. Movements of the head did not cause unsteadiness or apparent movements of test objects. The examiner could not observe any irregularities of the ocular movements or oscillations of the eyes when the head was in motion. Station was steady and gait normal. The only symptom was some little uncertainty when making rapid turns in dancing. There was of course complete loss of function of the right eighth nerve.

Comment. If a normal subject is placed in a Bárány chair and rotated from left to right, two distinct reactions are produced. During the period of acceleration of the movement, the eyes move slowly to the left and the quick phase of the nystagmus is to the right. As the rotation ceases and the movements of the patient's head are retarded, the nystagmus changes in direction, the slow phase of the movement being directed to the right and the quick movement being to the left. The second reaction which may be called the "after nystagmus," is, of course, the one which is observed in the routine clinical tests of vestibular function. The labyrinth towards which the head is rotated is stimulated more strongly, it is taught, than the labyrinth on the opposite side. Hence, in rotation to the right, the compensatory movements of the eyes to the left are due chiefly to the activity of the right vestibule. Rapid rotation of the head, twenty times or more, is obviously an unusual experience and in the routine of our daily life we rotate our heads at relatively slow speed, and perform only one movement at a time. It seems clear that the nystagmus during rotary acceleration is the expression of a physiological mechanism by which ocular fixation is maintained. In the first two cases abstracted above these vestibulo-ocular movements were demonstrated with great ease, due to the fact that volitional movements of the eyes in one or more planes were lost and the reflexes were, therefore, uncovered and perhaps exaggerated. In the third and fourth cases, all the vestibulo-ocular reflexes were abolished and their absence made it impossible for the patient to fix objects accurately while his head was in movement, despite the fact that he preserved normal volitional movements of the head and eyes. In the fifth and sixth cases only the right eighth nerve was destroyed, and so the symptoms were pronounced only when the head was turned sharply to the right.

Mowrer (2) has recently presented evidence derived from the study of normal subjects which indicates that the vestibular reflexes are

utilized in maintaining ocular fixation during movements of the head. His paper should be consulted in the original.

CONCLUSIONS

1. A case is described in which there was complete loss of all volitional movements of the eyes due to supranuclear lesions. Appropriate vestibular stimulation caused tonic deviation of the eyes in any desired plane, but there was no nystagmus. The eyes could be moved freely by passive movements of the head during ocular fixation.

2. A second case is described in which severe left hemiplegia was associated with loss of left lateral gaze. The eyes could, however, be moved into the extreme left lateral position by passive movements of the head to the right while the patient was fixing. Irrigation of the right ear with cold water produced tonic deviation of the eyes to the right, but there was no quick compensatory movement to the left and, hence, no nystagmus.

3. Two cases are presented in which section of both vestibular nerves caused abolition of the vestibulo-ocular reflex, leaving volitional movements of the head and eyes intact, but causing loss of ocular fixation during movements of the head.

4. Two cases are given in which the right eighth nerve was sectioned with the result that for a time ocular fixation was imperfect when the head was turned sharply to the right.

5. We believe that these observations indicate that the slow phase of induced vestibular nystagmus is the expression of a vestibulo-ocular reflex which, under physiological conditions, is essential for accurate fixation of the eyes during movements of the head. This reflex is most easily demonstrated by slow passive movements of the head in cases of paralysis of conjugate ocular movements.

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A CLINICAL STUDY OF THE CONTROL OF THE BLADDER BY THE CENTRAL NERVOUS SYSTEM[1]

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INTRODUCTION

A study of the disturbances of micturition which are associated with injury of the nervous system in man has led us to attempt to differentiate characteristic physiological changes associated with injury of particular groups of cells or fibers. The classification set forth here is an anatomical one; thus syphilis, disseminated sclerosis, or arteriosclerosis injuring both cortico-spinal tracts produce similar findings. The difficulty lies in discovering cases in which one tract in the nervous system is involved, and the others are functioning normally. The examples have been chosen from some 200 cases as typical for illustration. There are probably other characteristic types of change of which we have as yet no example. The effect of section of the sympathetic fibers to the bladder has been studied experimentally in the cat (Langworthy, Reeves and Tauber, 1934), but we have no records illustrating this isolated lesion in man.

The experiments record the responses of the smooth muscle of the bladder wall and also the intravesical pressure at the time when the sphincters relax. Denny-Brown and Robertson (1933) have shown clearly that micturition is initiated by a contraction of the bladder muscle, and that the relaxation of the sphincters is secondary to this contraction.

METHODS

The methods of obtaining graphic records of vesical function have been discussed in detail in previous papers (Lewis, Langworthy and

[1] This study of the control of the bladder by the central nervous system was supported by a grant from the National Research Council.

Dees, 1935). A catheter is inserted into the bladder through the urethra and is connected by a T-tube with a source of fluid and a recording mechanism. The apparatus which we use is quite simple and can be sterilized. We lay stress on the use of an air-water system in the recording apparatus. This has less inertia than mercury and records accurately slight changes of intravesical pressure and small waves of muscle contraction. The pressure in the bladder is observed during filling as seen in a glass tube which rises six feet above the level of the

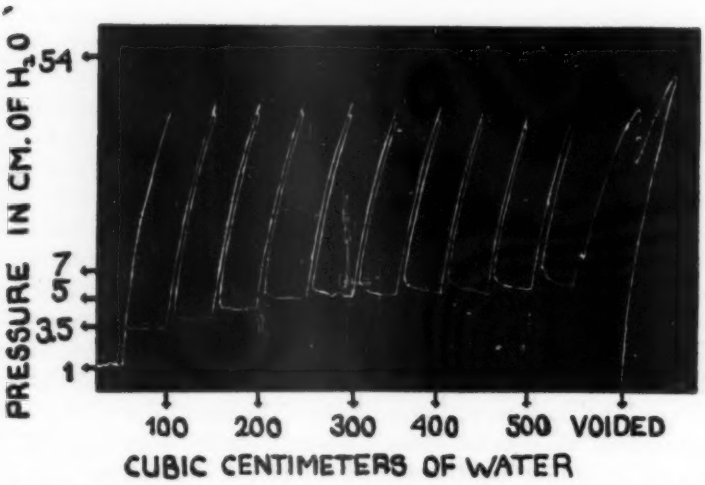

FIG. 1. Graphic record of normal bladder filling. Fluid was introduced into the system in equal quantities of 50 cc. each. The intravesical pressure remained below 7 cm. of water until filling was complete. At a capacity of 500 cc. the pressure rose to 54 cm., and fluid escaped around the catheter.

symphysis pubis. This vertical tube also prevents fluid from escaping into the tambour when the pressure rises. The patient is asked to remain quiet during the preparation of the record since any speech or movement is recorded upon the drum. Because of the difficulty in setting the zero point of the manometer, the pressure readings have only an approximate accuracy. The graphic records give a continuous picture of bladder activity.

NORMAL READING

A series of records has been obtained from normal individuals who complained of no vesical or neurological symptoms; one of these graphs is shown in figure 1. The normal bladder has a capacity of about 500 cc. Usually, fluid was introduced in equal quantities of 50 cc. After the fluid had entered, the flow was stopped and the vesical pressure allowed to fall to a resting level. The vertical lines upon the graph record the sharp rises of pressure associated with the sudden entrance of fluid into the system. The pressure in the empty bladder was 1 cm. of water. The pressure was 3.5 cm. when the bladder held 50 cc. and remained below 7 cm. until 500 cc. had been introduced and filling was completed. After each quantity of fluid had entered the bladder, the pressure dropped at once to a resting level and maintained it. No waves of muscle contraction occurred during the filling. At a 250 cc. volume, the subject became first aware of vesical distention, and the slight irregularity in the curve at this point was associated with the act of speaking. The pressure was slow in reaching a resting level on a 500 cc. volume. A marked contraction of the muscle raised the pressure to 54 cm.; at this time fluid escaped from the urethra around the catheter. The rise of pressure was not a smooth curve owing to the effort of the patient at one point to stop the muscle contraction.

BLADDER FUNCTION AFTER INJURY TO THE POSTERIOR SACRAL NERVE ROOTS—THE TABETIC BLADDER

Clinicians who have made records of vesical activity are most familiar with the characteristic abnormalities found in cases of tabes dorsalis (Rose and Deakin, 1929, and Muschat, 1935). Recent experiments with cats showed that these changes are dependent upon section bilaterally of the second, third, and fourth posterior sacral roots (Dees and Langworthy, 1935). Section of the lumbar posterior nerve roots fails to produce them. Nor can they be duplicated experimentally by section of the posterior columns of the spinal cord. The sensory impulses from the bladder travel upward in the lateral columns of the cord (Barrington, 1933).

Patients with tabes dorsalis exhibit urinary disturbances which are characteristic of the disease. The histories of 278 patients with tabes

dorsalis were examined to learn the bladder symptoms of which they complained. All stages of the disease were represented. Urological symptoms were found in 140 individuals of this group. Incontinence of urine occurred in 83, and hesitancy in starting micturition in 71. Nocturnal incontinence was a prominent feature in 22 patients. Nineteen had developed acute urinary retention. Almost all of the individuals with urinary symptoms had suffered from severe pains in the legs at some time during their illness. In many there were areas of cutaneous sensory loss over the region supplied by the sacral posterior roots. Severe attacks of lancinating pain in the bladder, vesical crises,

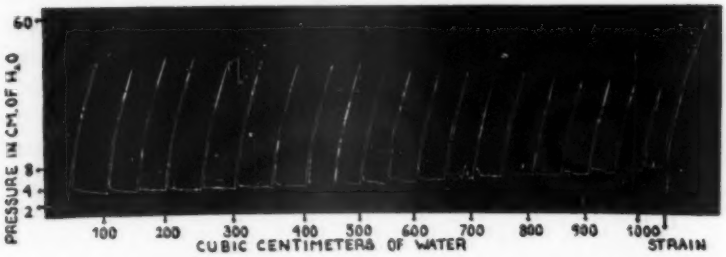

FIG. 2. This record of vesical filling was made from a patient with tabes dorsalis who complained of hesitancy. Filling was stopped at 1000 cc. The patient was able to raise the pressure to 60 cm. of water, but the contraction was not sustained. The resting intravesical pressure was low.

occur infrequently, and are due to irritation of the posterior roots carrying vesical sensation.

The vesical abnormalities are dependent on a loss of perception of bladder distention due to injury of the sensory nerve fibers. The poor functioning of the muscle which follows an interruption of the primary reflex arc is made worse by the stretching of the wall. Weak contraction of the muscle causes slowness in initiation of micturition and loss of strong expulsive force. The incontinence which is more common at night is probably a true overflow incontinence. Since the muscle does not contract to expel all the urine, a residuum gradually collects.

A typical record from a case of tabes dorsalis with hesitancy and incontinence is given in figure 2. This bladder held 1000 cc. without

discomfort; filling was arbitrarily stopped at this point because we did not wish to subject the muscle to further stretching. The pressure in the empty bladder was recorded as 2 cm. of water. With the introduction of 50 cc. the pressure rose to 4 cm. and remained below 8 cm. until the bladder held 1000 cc. The pressure fell immediately to a resting level after each addition of fluid. The only slight irregularities of the curve at a capacity of 650 cc. and 750 cc. were the result of the patient's speaking. With 1000 cc. in the bladder, the subject was asked to attempt micturition. The pressure rose to 60 cc. but this rise could not be sustained and no fluid escaped around the catheter.

BLADDER FUNCTION IN CASES OF SPINA BIFIDA

Spina bifida occurs commonly in the lumbosacral region and is associated with abnormalities of the sacral cord and its nerve roots. Disturbances of micturition occur in these patients. From the embryological point of view, spina bifida is dependent on some failure of development of mid-line structures and closure of the neural tube. There may actually be a distortion of the sacral portion of the spinal cord. More commonly the nerve roots are caught in scar tissue which develops in the neighborhood of the abnormality. In cases of spina bifida occulta, the cause of the urinary symptoms is not immediately apparent. A tumor can often be palpated in the region of the bony defect.

Examination of the last 500 x-ray plates of the lumbosacral region taken at the Brady Urological Institute revealed that in 183, or 36.6 per cent, there was some failure of fusion of the lumbosacral vertebrae. This number did not include abnormalities of the fourth and fifth sacral vertebrae alone.

The records of bladder function in patients with spina bifida can be separated into two groups depending on whether the motor or the sensory roots are predominantly injured. An example of each type is given. Neurological examination confirms the extent of motor and sensory involvement.

D. F. was a white male, 6 years of age. He never gained voluntary control of the bowels or bladder. Small amounts of urine were voided frequently, and there was dribbling at the end of micturition. Residual urine at times amounted to 400 cc. The right leg was shorter than the left, and its muscles were smaller.

No other motor abnormalities and no sensory changes could be demonstrated. In the right posterior gluteal region a fatty fibrous mass was felt which communicated with a defect in the laminae of the lumbar vertebrae. The x-ray showed a failure of closure of the fourth and fifth lumbar vertebrae and of all the vertebrae below this level.

Figure 3 is a record of the vesical activity. Fluid escaped from the urethra at volumes of 200 and 250 cc.; the pressure rose to 93 cm.

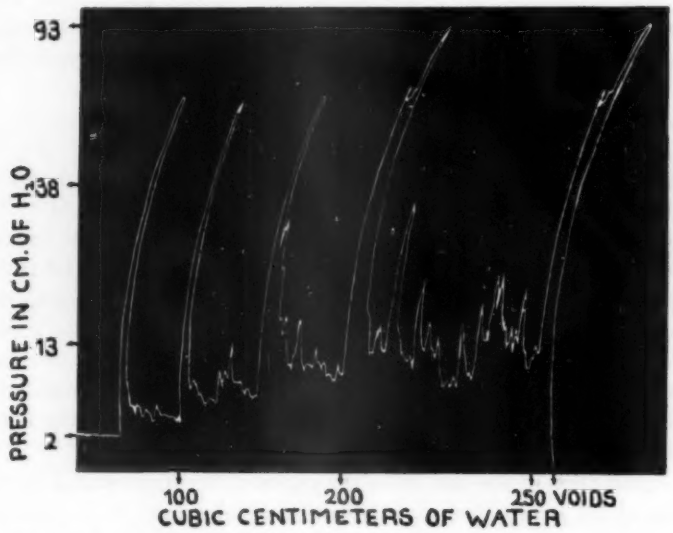

FIG. 3. The patient had a spina bifida with involvement of the anterior sacral roots. Vesical contractions occurred at irregular intervals. They were weak and of short duration.

The characteristic features of the curve were waves of vesical contraction occurring throughout the period of filling. These varied in force and consequently in amplitude (as seen in the record), and were poorly sustained. They tended to become stronger as filling progressed. After the introduction of fluid, the pressure was rather slow in falling to a resting level; this was particularly shown at 150 cc. volume. When 200 and 250 cc. had entered the bladder a contraction of the muscle occurred before the pressure fell. This illustrates a

response of the muscle to sudden stretching. With each of these contractions urine escaped. Since the contractions persisted for only a brief period, only a small amount of urine was voided at one time. Experiments have shown that these small contractions can be elicited from the vesical muscle and the intrinsic nerve plexus after the parasympathetic fibers are destroyed.

The second example of vesical abnormality associated with spina bifida reveals a greater injury of the sensory than of the motor fibers.

A white man of 63 noticed some urgency of micturition 18 years ago. There was mild dribbling and occasional frequency. Hesitancy and difficulty in starting the stream had been present for 8 years. There was interruption of micturition, and the stream lacked force. He thought he did not empty the bladder com-

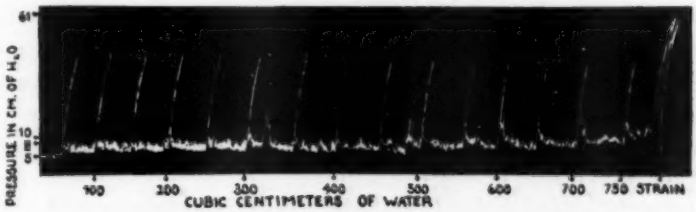

FIG. 4. This patient had a spina bifida with predominant involvement of the posterior roots, but the anterior sacral roots were also damaged. The record is similar to that obtained from the patient with tabes dorsalis, except that small contractions of the muscle are seen.

pletely. He was cystoscoped, and the bladder was found to be dilated and to have poor tone. Seven years ago the residual urine was 1500 cc. Ten months ago he became unable to void.

Examination showed a round, soft, elastic swelling about 5 cm. in diameter and suggesting a lipoma, in the dorsal midline over the upper portion of the sacrum. Palpation beneath this mass revealed a defect in the laminae of the vertebrae and this defect was confirmed by an x-ray. There was cutaneous anesthesia over the buttocks and the back of the thighs. The ankle jerks could not be obtained. The anal sphincter had poor tone. There was some obstruction to micturition due to intra-urethral hypertrophy of the lateral lobes of the prostate.

The bladder had a capacity of 750 cc., as shown in figure 4. The pressure was 5 cm. with the bladder empty and remained below 10 cm. until filling was complete. In the early stages of filling, the pressure fell quickly to a resting level. At 750 cc. the patient was asked to micturate. He raised the pressure to 61 cm. but was unable to maintain the contraction.

These findings suggest a lesion of the posterior sacral roots as found in cases of tabes dorsalis. In addition, small waves of vesical contraction occurred throughout filling and became more marked as the volume was increased. The muscle also responded to stretching, particularly at 300 cc. volume. These waves are never present after injury of the posterior roots alone and indicate damage of the anterior motor sacral roots. On the basis of this record and the neurological examination, the conclusion was reached that the posterior roots were predominantly, the anterior roots slightly injured. Pure obstruction due to prostatic hypertrophy never gives rise to changes of this kind. Indeed the prostate was removed from this patient, and four months later there was no change in the record of vesical activity.

BLADDER FUNCTION AFTER DAMAGE TO THE CORTICOSPINAL TRACTS

The authors have dealt with the changes in vesical function after damage to the corticospinal tracts in detail in a previous report (Lewis, Langworthy, and Dees, 1935). Here it is only necessary to give a summary of the findings and a typical example to carry the argument.

Langworthy and Kolb (1933) found in acute experiments with cats that removal of one cerebral motor cortex caused a marked decrease in bladder volume. Removal of both cortices produced a greater decrease in volume. Later the cerebral motor cortices were stimulated and the behavior of the bladder noted (Langworthy and Kolb, 1935). This stimulation produced a fall in intravesical pressure followed, if stimulation was continued, by a sharp rise, initiating micturition. Responses could be obtained more easily from one cortex than the other, and usually the left was the more responsive. It was suggested that one cortex was dominant in bladder control.

Eleven patients with bilateral injury of the corticospinal tracts were studied. They complained of urgency, frequency, and incontinence. The bladder capacity was reduced to as little as 50 cc. The stretch reflex was hyperactive so that the introduction of fluid produced waves of vesical contraction. The final contraction which initiated micturition was sudden and strong, raising the pressure to levels above those observed normally. The resting intravesical pressure was often somewhat higher than normal. The abnormalities were largely dependent upon the increased activity of the stretch reflex.

Seventeen patients with unilateral corticospinal injury manifest as a hemiplegia were examined. Six of these suffered from a left-sided paralysis and eleven from a right. The six subjects with a left hemiplegia had a bladder of somewhat less than average volume. The

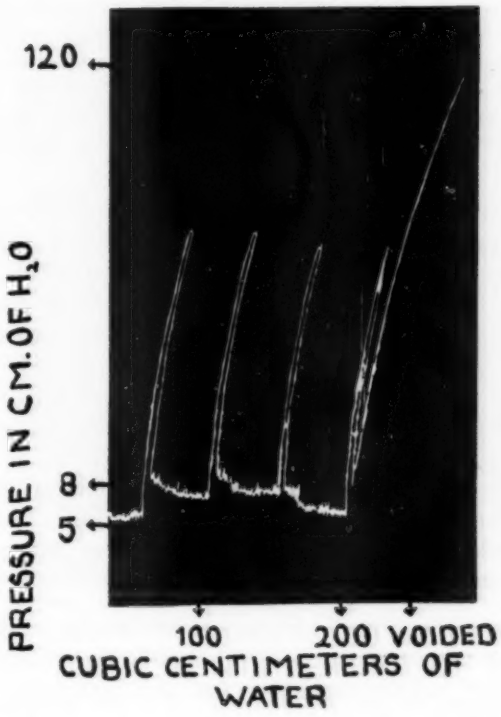

FIG. 5. The patient showed evidence of bilateral injury to the corticospinal tracts. The bladder had a small capacity. The resting intravesical pressure was high. The contraction of the muscle was strong.

records of these all showed characteristic changes in that small waves of vesical contraction occurred throughout filling. The stretch reflex was slightly hyperactive. Ten of the eleven patients with a right hemiplegia had a bladder of much less than normal capacity. In these cases the stretch reflex was very hyperactive. These findings

suggest that one hemisphere is dominant in bladder control, and this dominance is on the left side in right-handed individuals.

The case selected as an example (fig. 5) shows the effect of bilateral loss of corticospinal control.

A colored male, 52 years of age, noticed weakness of the left arm and leg eleven months ago. Later the same trouble developed on the right side. He became unable to stand or walk. There was urgency, frequency, and incontinence. The muscles of the arms and legs showed loss of strength and spasticity. All the deep reflexes were hyperactive. There were bilateral Hoffmann and Babinski reflexes and bilateral ankle clonus. Some abnormalities of sensation were demonstrated in the legs.

The record of vesical activity is shown in figure 5. The resting pressure in the empty bladder was high,—5 cm. of water. At a capacity of 50 cc. the pressure was 8 cm. and remained at this level until filling was complete. The pressure was slow in returning to a resting level after additional quantities of fluid had entered the bladder. A strong contraction of the muscle occurred as the result of increasing the volume to 200 cc. This raised the pressure to the abnormal height of 120 cm. of water, and fluid escaped around the catheter. This contraction was initiated by stretching.

The curve illustrates the abnormalities found after bilateral injury of the corticospinal fibers and manifested as small capacity, hyperactive stretch reflex, unusual strength of contraction, slow accommodation to increased volume, and a relatively high resting pressure.

BLADDER ABNORMALITIES RESULTING FROM LESIONS OF THE SPINAL CORD INVOLVING THE PATHWAYS FROM THE CEREBRAL CORTEX AND MID-BRAIN BILATERALLY

Experiments have shown that the tone of the vesical musculature is controlled by reflex arcs extending into the upper portion of the mid-brain (Langworthy and Kolb, 1933 and 1935). After bilateral injury of the corticospinal fibers, these reflex arcs are released just as are those controlling tone in striated muscle. The stretch reflex becomes hyperactive and the bladder capacity is decreased. No isolated lesions of the mid-brain fibers have been recognized. The fibers from the mid-brain run close to the corticospinal fibers in the lateral columns of the spinal cord where the two groups may be injured bilaterally.

We have already described some examples (Lewis, Langworthy and Dees, 1935) and give one more to complete the story in this paper (fig. 6).

The patient, a white male of 22, developed numbness and tingling in the lower portion of the body in April, 1935. The legs became weak. Urgency of micturition appeared and became so marked that he had to empty the bladder every half

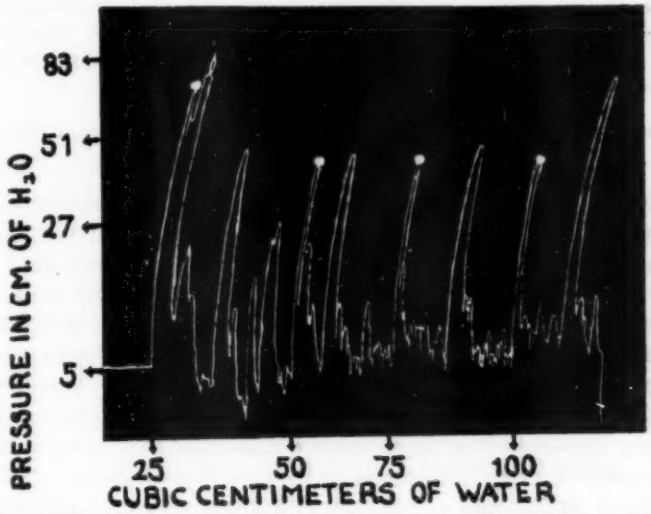

FIG. 6. This patient with disseminated sclerosis had signs of bilateral involvement of the lateral columns of the spinal cord, which injured the corticospinal fibers and probably the efferent pathways from the mid-brain. Waves of bladder contraction of good strength but short duration occurred throughout filling. The lines capped with white dots indicate the times when fluid was introduced.

hour during the day and get up several times at night. Incontinence occurred if he did not micturate at once. The stream was weak, and there was dribbling at the end of micturition. Sexual activity was abnormal in that there were normal erections but no emissions.

Examination revealed pallor of both optic discs. The gait was unsteady and spastic. The Romberg test was positive. Vibratory sense was impaired in both legs. The knee and ankle jerks were hyperactive, and there were bilateral Babinski reflexes.

The graphic record in figure 6 represents vesical activity. The vertical lines

capped with white dots indicate the points at which 25 cc. quantities of fluid were injected. The pressure in the empty bladder was high,—5 cm. of water. After the first quantity of fluid entered the bladder, there was a marked contraction of the muscle in response to the stretching. Thereafter waves of contraction of variable strength and short duration occurred at irregular intervals. Voluntary effort on the part of the patient did not control these contractions. He was uncomfortable each time the pressure rose and complained of urgency of micturition even when the bladder held as little as 25 cc. As further fluid was added, the contraction waves continued. With 100 cc. in the bladder, a powerful wave raised the pressure to 83 cm., and some fluid escaped around the catheter. The patient was distressed, and the test was terminated. The contractions were of short duration and never sustained.

ABNORMALITIES OF MICTURITION ASSOCIATED WITH BASAL GANGLION LESIONS AND THE PARKINSONIAN SYNDROME

Certain patients with the parkinsonian syndrome complain of frequency of micturition. In cases where this is a symptom it causes considerable distress. The out-patient histories are not ideal for statistical work, inasmuch as the bladder abnormalities were not stressed. Of 132 patients with chronic encephalitis, 14 complained of frequency of micturition and 2 of urgency. Eleven had nycturia three or four times. Inasmuch as most of the patients were young adults, the nycturia is significant as having a neurological basis. Frequency was dissociated from urgency of micturition. None of these cases showed evidence of injury of the corticospinal fibers. Another group of 81 histories of patients with arteriosclerotic parkinsonian disease or paralysis agitans were examined. Fifteen of these patients complained of frequency of micturition and 18 had nycturia. Nycturia in these older patients is not significant for our study. Only 3 of those who complained of frequency were aware of urgency of micturition.

Patients with the parkinsonian syndrome are known to show abnormalities of function in glands and smooth muscle as well as in striated muscle. There is an oversecretion of glands manifested by increased salivation, sweating, greasiness of the face and, in one case which was seen recently, excessive lacrimation. Vague complaints of fullness and pain in the abdomen after meals suggest involvement of the smooth muscle of the gastro-intestinal tract.

Micturition was studied in patients with the typical changes in

striated muscle whether they complained of disturbances of micturition or not. One typical example is used for illustration (fig. 7).

A white man of 56 observed tremor of the right arm eleven years ago. Three years later the tremor spread to the left arm and to the legs. He noticed slowness and difficulty of movement. Examination showed a man with an expressionless face and stooping posture. The voice was low, slow and monotonous. There was a loss of associated movements in walking. A coarse regular tremor was present in the arms and to a less extent in the legs. The deep reflexes were

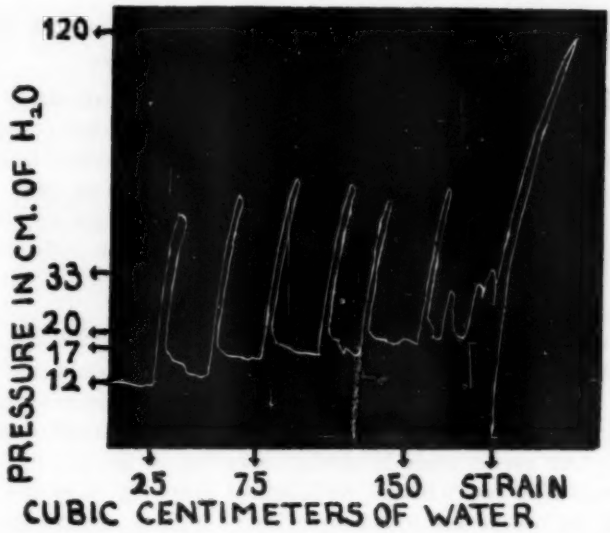

FIG. 7. Record made from a patient with the parkinsonian syndrome. The resting pressure in the empty bladder and during filling was abnormally high. The capacity was small.

normally active. There were no Hoffmann or Babinski reflexes. He had to empty the bladder every two hours during the day and three or four times at night.

The external sphincter was resistant to passage of a catheter. Figure 7 shows the record of vesical filling. The pressure in the empty bladder was 12 cm. of water. Fluid was introduced in quantities of 25 cc. each, and the capacity was reached when the bladder held 150 cc. The pressure then rose to 120 cm., and fluid escaped around the catheter. During the period of filling the resting pressure was 12 to 20 cm. of water. The pressure returned fairly quickly to a resting level after fluid was added. There was no evidence of hyperactivity of the stretch reflex.

This curve shows two marked deviations from the normal. The resting pressure was high both in the empty bladder and during filling, and the capacity was decreased. The stretch reflex was normally active. The emptying pressure was higher than normal. These changes are so characteristic that we consider them typical for the parkinsonian patient. These two were not both present in every patient examined but were seen in those who complained of vesical symptoms.

BLADDER ABNORMALITIES CHARACTERISTIC OF LESIONS OF THE CEREBELLUM OR CEREBELLAR PATHWAYS

Holman (1926) observed that cerebellar tumors, particularly those located in the mid-line or those which distorted mid-line structures, produced abnormalities of micturition. There was marked hesitancy for as long as 1 to 10 minutes or complete retention of urine. The difficulty was not permanent but occurred at intervals for varying periods of one to seven days after which micturition again became normal. Occasionally incontinence developed and continued. Holman gave detailed reports of 8 cases seen by him.

Three possible explanations for the difficulty of micturition come to mind. The tumor may have pressed upon the medulla and interfered with pathways from the cerebral cortex or mid-brain which normally control micturition. This was the explanation accepted by Holman. Our curves made in similar cases (fig. 8) are not like those observed after injury of the corticospinal fibers (fig. 5) or like those which we believe are found after injury both of the corticospinal tracts and the pathways from the mid-brain (fig. 6). Moreover Holman was careful to point out in each of his protocols that there was no evidence of involvement of the corticospinal fibers. The motor changes in the extremities were those characteristic of damage to the cerebellum.

The two other possibilities require greater consideration. The changes in micturition may be a manifestation of the great increase in intracranial pressure which is present. The final explanation suggests that damage to the cerebellum itself produces the changes in the function of micturition. We present evidence to support this third hypothesis.

Holman made no records of vesical activity. In our example (fig. 8)

the bladder shows a large capacity and low resting pressure during filling. The bladder was not filled to capacity, but the experiment was terminated at 1000 cc. The record was very similar to others obtained from patients with tabes dorsalis (fig. 2). The abnormalities in tabes are caused by the loss of tone in the vesical muscle due to damage to the posterior sacral roots. In Holman's cases the symptoms were those of which tabetic patients complain. Holman stated that there were no disturbances of cutaneous or deep sensation in his patients. Could the loss of tone in the bladder muscle be dependent on the injury to the cerebellum? Tone in the striated muscle of man is decreased after cerebellar injuries.

A patient with a large neoplasm growing in the cerebellum near the mid-line was studied in regard to vesical activity. The position of

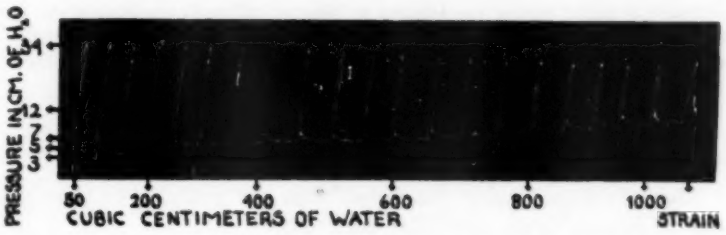

FIG. 8. This patient had disseminated sclerosis with symptoms largely dependent on involvement of the cerebellar pathways. The filling was stopped at 1000 cc. He was able to raise the pressure to only 34 cm. of water.

the tumor was confirmed at postmortem examination. He suffered from hesitancy of micturition and later from complete retention. The graphic record of bladder filling showed a large capacity and low resting pressure similar to that in figure 8. The factor of increased intracranial pressure was not excluded in this case.

Patients with disseminated sclerosis often show predominant symptoms of involvement of the cerebellar tracts. They do not have increased intracranial pressure. They complain of hesitancy and retention. One of these was chosen as an example of disturbances of micturition after injury of the cerebellum or its pathways.

A white male of 27 began to notice awkwardness of his arms and legs five months ago so that he had difficulty in picking up objects or in walking. He was unable to keep his balance, and people thought that he was intoxicated. Vision

became blurred in the right eye. His legs became weak and easily tired. During the entire illness there had been hesitancy of micturition so that he had to wait two or three minutes. He emptied the bladder two or three times a day.

A horizontal nystagmus could be demonstrated on looking to either side. Speech was monotonous, and there was some slurring of the test phrases. Tone was decreased in the arms and legs. An ataxia which was greater on the left could be demonstrated on finger-nose test. The heel-knee test was poorly performed on both sides. The gait was staggering; there was a slight Romberg response. The deep reflexes were hyperactive, especially in the legs. The Hoffmann reflex was positive bilaterally. There was ankle clonus on the left, and a positive Babinski reflex was present on the right. Over the cutaneous area supplied by the sacral segments of the cord, sensation was normal. Cerebellar symptoms predominate over corticospinal symptoms in this case.

Figure 8 shows the record of vesical activity in this patient. The pressure in the empty bladder was zero; the pressure remained between 3 and 12 cm. of water during filling. The resting level was quickly regained after the addition of each quantity of fluid. Filling was stopped at 1000 cc., although the bladder seemed capable of holding a larger quantity. The patient was then asked to attempt micturition. The resultant vesical contraction raised the pressure only to 34 cm. of water, and no fluid escaped around the catheter.

Watts and Uhle (1935) describe similar findings in a patient with a left acoustic neurinoma giving symptoms of cerebellar injury.

These findings support the theory that the vesical symptoms are due to damage to the cerebellar pathways.

DISCUSSION

The discussion of tone and its abnormalities has been avoided in our studies of the bladder unless the term was qualified. Holmes (1933), describing the behavior of the paralyzed bladder after injury to the spinal cord, stated that it behaved at first as an inert elastic bag. Later, "the bladder had to some extent acquired again the property of adapting its size to its contents; its muscular wall had evidently regained some tone." Denny-Brown and Robertson (1933) have likewise been precise in their statements concerning vesical tone.

Other workers have used the words hypertonus and hypotonus as regards the bladder in a vague way. The reflexly active automatic bladder after transection of the spinal cord above the sacral segments has been referred to as a hypertonic bladder. A large bladder has been called hypotonic and a small bladder hypertonic.

The records given here have certain objective criteria by means of which it is possible to discuss tone in the urinary bladder. These are the capacity, the ability to accommodate to increased volumes, the resting pressure in the bladder empty and during filling, and the response of the muscle to sudden stretching. The power is measured by the strength, duration, and spacing of muscle contractions, and by the pressure which must develop before fluid escapes from the urethra.

After injury of the posterior sacral roots or of the cerebellum (figs. 2 and 8), the capacity of the bladder is increased, the wall reacts quickly to accommodate a greater quantity of fluid, and the resting pressure is low in the empty bladder and during filling. No responses of the muscle to stretching are recorded in filling the bladder to 1000 cc. capacity, at which point the test was terminated in both cases. On the basis of these findings, it may be concluded that tone in the smooth muscle of the bladder wall is decreased after injury of the posterior sacral roots or of the cerebellum.

The power of vesical contraction is also impaired. The patient with tabes dorsalis was asked to attempt micturition with 1000 cc. in the bladder. He raised the pressure to 60 cm. but the contraction wave was not sustained. Nor was it strong enough to force fluid from the urethra around the catheter. The patient with cerebellar abnormalities was able to raise the pressure voluntarily to only 34 cm. of water. The contraction wave again was poorly sustained, and no fluid escaped from the urethra.

The changes in the bladder following corticospinal tract injuries are shown clearly in a group of graphs dealing solely with this abnormality published in another place (Lewis, Langworthy and Does, 1935). They show particularly well the increased responses of the vesical muscle to stretching. The bladder capacity is decreased to as little as 50 cc. in examples which have been given previously and to 200 cc. in the case described here (fig. 5). There is slow and faulty accommodation to increasing quantities of fluid. The resting pressure in the empty bladder and during filling is usually high, although it may approximate the normal. Tone is increased in smooth muscle just as in striated muscle after injury of the corticospinal tracts, particularly if the damage is bilateral

The contractile power of the muscle appears to be strong, inasmuch

as the pressure rises to abnormally high levels. This strong contraction may be developed to overcome the increased tone of the external sphincter. The duration of the contraction is usually sufficient to empty the bladder around the catheter. There may be deficiency in the duration of the contraction wave, but these patients seldom show residual urine. The contraction gains efficiency in that the capacity is small.

These changes are dependent on the increased responses to stretching. There is no longer voluntary power of controlling the contraction waves. The strength of the waves produces the complaint of urgency, and the small vesical capacity gives rise to frequency.

Just as the tone and contraction in the striated muscle of parkinsonian patients differ from those in hemiplegia or paraplegia, so the abnormalities of vesical activity are different (fig. 7). The vesical capacity is small. The ability to accommodate to increased volumes of fluid is impaired. The resting pressure in the empty bladder and during filling is abnormally high. The normal individual feels a desire to micturate before the intravesical pressure reaches 10 cm. of water. The pressure in the empty bladder of the parkinsonian may be 12 cm. of water and reach 20 cm. before filling is complete. A normal stretch reflex occurs at the end of filling, but no increased activity of the stretch reflex is seen.

The contractile power of the bladder raises the intravesical pressure abnormally high. Again, this may be developed to overcome the external sphincter. The contraction waves are well sustained so that the bladder is emptied completely, and no residual urine collects, Inasmuch as the response to stretch is not overactive, the complaint or urgency occurs seldom. The decreased vesical capacity leads to frequency of micturition.

Walshe (1929) stated that the tone in the striated muscle of patients with the parkinsonian syndrome is of unvarying intensity through the fullest possible range of shortening and lengthening. This appears to be true of the bladder in which the intravesical pressure is high when the bladder is empty and throughout filling. He showed that the tone was dependent on the reaction to stretching, but the stretch responses were not increased.

Three examples were given of more severe abnormalities of micturi-

tion. In one, bilateral plaques in the lateral columns of the spinal cord were thought to have injured the corticospinal tracts and also the efferent pathway from the mid-brain (fig. 6). Vesical contraction waves occurred irregularly during filling, but they were of short duration and therefore inefficient in emptying the bladder completely. The contraction waves were of even smaller amplitude as well as of short duration after damage to the anterior sacral nerve roots (fig. 3). The patient voided small quantities of urine frequently but never emptied the bladder. Finally, small contraction waves appeared during the filling of a bladder of large volume and low resting pressures (fig. 4). These waves at once denoted damage to the motor side of the reflex arc, the anterior sacral roots in this case.

There are no reliable methods for quantitative measurement of tone in the striated muscle of man. The graphic records of vesical activity do give rough quantitative information concerning the smooth muscle of the bladder.

The primary reflex arc of the autonomic nervous system is different anatomically from the primary somatic reflex arc. On the motor side the autonomic has two neurones, whereas the somatic motor has one. There is little information concerning the afferent impulses from the periphery which influence the preganglionic cells of the autonomic system. As regards the bladder, it seems clear from the experiments that the control of the brain over these two systems is similar.

SUMMARY

The tone and contraction of the smooth muscle of the bladder are controlled by reflex arcs in the central nervous system. The bladder holds large quantities of fluid at low pressure following injury of the posterior sacral roots. Small rhythmical waves of contraction occur throughout filling when the anterior sacral roots are involved. After injury of the corticospinal fibers the stretch reflex becomes hyperactive, and the vesical capacity is small. In many patients with the parkinsonian syndrome the intravesical pressure is abnormally high both in the empty bladder and during filling. The bladder holds only a small quantity. Lesions of the cerebellum or its pathways produce a large bladder with a low resting intravesical pressure. Both the corticospinal fibers and efferent fibers from the mid-brain, which con-

trol tone in the vesical muscle, may be injured by lesions in the lateral columns of the spinal cord. Frequent waves of vesical contraction occur but they are poorly sustained. There may be any combination of these anatomical lesions and resultant physiological changes. The characteristic abnormalities of bladder function may be recognized in the graphic records of vesical activity.

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THE DIAGNOSIS OF OBSCURE FEVER

I. The Diagnosis of Unexplained, Long-continued, Low-grade Fever

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INTRODUCTION

There is no other problem, of equal interest and importance, more often brought to the physician for solution than the diagnosis of obscure fever. The specific infections bear characteristic marks by which they may be recognized and, although frequently it is difficult to distinguish them readily, still after a period of careful observation their identity is usually disclosed. With this routine differentiation we are not now immediately concerned. Nor shall we dwell upon brief febrile episodes which happily subside in a few days or a few weeks even though a satisfactory diagnosis cannot be made. What we propose to discuss are circumstances under which fever may last for weeks, months or even years, and in spite of the most careful investigation no satisfactory explanation for the abnormality be discovered. Often, at the end, characteristic clinical manifestations develop which establish the correct diagnosis; sometimes the cause is exposed at operation; at other times it remains hidden until revealed by the postmortem examination; at yet other times, even after years of patient study, the fever persists unabated and still unexplained.

The problem is a familiar one to every physician. It is his almost daily task to attempt its solution. There is scarcely ever a time when there is not at least one patient on the medical wards of each large hospital with an unexplained fever, and in the consulting office they are met with just as frequently. Whenever physicians gather together to gossip and talk over the amusing and puzzling details of practice, instances of obscure fever are nearly always brought up for comment and discussion. However, in spite of this universal interest, the sub-

ject is seldom dealt with as an independent topic and in a comprehensive way. Nevertheless, we think that its importance well merits such independent treatment. Dyspnea, cyanosis, edema, auricular fibrillation, jaundice, ascites and other symptoms too numerous to mention are frequently discussed apart from the disorders of which they are conspicuous manifestations. Obscure fever may be considered profitably in the same way. There are many questions concerning it that we should like to have answered, and accurate answers would guide our observations and help us in specific instances to arrive at the correct diagnosis. When patients with obscure fever are followed for a long time, what does the disease finally turn out to be? Are there any accompanying features occurring sufficiently often to give us a clue as to which of these diseases is probably at fault? Do the height of the fever, the age of the patient and the duration of symptoms have a bearing upon diagnosis?

Our interest in this subject was freshly aroused a short while ago when an unusually puzzling instance of obscure fever was at last correctly diagnosed by a fortunate comparison with a similar instance observed a few years before. The success of this empirical inference led us to recall many previous occasions upon which we had been equally puzzled over patients with unexplained fever, and we determined to gather together the records of these experiences so that we might see if any diagnostic lessons could be learned for future guidance. What promised to be a simple study has been surrounded by unforeseen difficulties which, however, with a little forethought, might have been anticipated. Cases which for months may have excited interest on account of unexplained fever are usually at last diagnosed either clinically or at autopsy and the records are then filed away under appropriate headings. Even when a satisfactory diagnosis cannot be made, a presumptive diagnosis is usually registered, and owing to this routine procedure all of the uncertainty that may have attended the course of the disease while under observation is lost, buried beneath uninforming markers.

In the face of these difficulties, therefore, we have been obliged to tax our memories and the memories of our associates to ferret out clues to even a small number of the many instances of unexplained fever which have been observed upon the wards of the Johns Hopkins

Hospital and in our private practice. In this laborious way we have slowly collected ninety cases which will be the basis of our report. The article will not be the comprehensive analysis we had hoped to make it. It is only a desultory fragment of what we had planned. Nevertheless, the interest and importance of the subject may serve as its justification and perhaps it will answer as an introduction to a subject which deserves to be more thoroughly treated.

The group of cases we have selected is unsuitable for statistical manipulation because the number is small and each case characterized by its own peculiar features. There are no common data to be appraised since the problem presented by any given case is individual and differs from the problems raised by each of the others. Almost every one supplies a pregnant text upon which might be preached a separate clinical sermon. We regard them with affectionate interest because we have personally labored to understand and solve their difficulties and they have become important stones in the edifice of our own clinical experience. They are fruitful illustrations of what we shall have to say, not units of statistical calculation. That so many behaved in this way and so many in that is unimportant; the vital lesson is in the individual behavior of each. The brief statistical matter we shall quote is merely a *résumé* of our own observations and in no sense a prediction of how the experience of others may turn out.

A search of medical literature has not rewarded us with abundant information about the diagnosis in cases of obscure fever. The information no doubt is there, but most of it is scattered and must be sought in case reports and in discussions of obscure diseases generally accompanied by fever. Here and there is found a clinical lecture with illustrative cases with comments upon the conditions most often causing the fever (1). However, we have found two papers which are based upon an analysis of a large number of cases and are important not only because they are unique but also because the observations and conclusions are in themselves valuable.

Alt and Barker (2), in reviewing the records of the Peter Bent Brigham Hospital at Boston, found that the diagnosis "Fever of Unknown Origin" had been made 173 times in their 34,000 consecutive medical admissions. Information was sought about what had happened to these 173 patients after leaving the hospital. The after-discharge

histories of 101 were obtained. Even with this additional information no definite diagnosis could be reached in 78. These 78 patients may be divided conveniently into three groups.

1. In 42 the fever had been of less than 10 days' duration.
   38 had remained well.
   1 had subsequently developed hypertensive vascular disease.
   1 had subsequently developed acute nephritis.
   1 had subsequently developed acute appendicitis.
   1 had died of some unascertained cause.
2. In 18 the fever had lasted for a period of 10 days or more, but had then subsided, the patients leaving the hospital afebrile and well.
   15 had remained well.
   1 had subsequently developed phlebitis.
   1 had subsequently developed subdeltoid bursitis.
   1 was found 6 years later to have rheumatic aortic insufficiency.
3. 18 patients were observed for an average period of 10 weeks and left the hospital with the fever still persisting.
   11 had become entirely well. 3 of these may have had Malta fever.
   2 still had fever of unascertained cause.
   5 had died in from 6 weeks to 4 years after leaving the hospital
      2 probably of malignant disease.
      1 probably of bacterial endocarditis.
      1 probably of some form of sepsis.
      1 had died finally of an acute streptococcus infection of the throat.

For the remaining 23 patients the following diagnoses were finally reached:

In 6, tuberculosis: 3 pulmonary, 1 miliary, 1 of caecum, 1 of salpinx.

In 6, rheumatic fever. This diagnosis was made upon the evidence of valvular heart disease developing subsequently.

In 3, carcinoma.

In 2, lymphoblastoma.

In 1, leukemia (aleukemic form).

In 1, hyperthyroidism.
In 1, appendicitis, verified at operation.
In 1, psoas abscess.
In 1, syphilis, identified by the therapeutic test.
In 1, malaria, identified by the therapeutic test.

Kintner and Rowntree (3) analyze the clinical records of 100 patients with long-continued, low-grade fever carefully studied at the Mayo Clinic from June 1919 to June 1930. Two-thirds of the patients were between the ages of twenty and forty years. Seventy-two were females, twenty-eight males. The average duration of the fever before the patients came to the Clinic was 17.6 months. The diagnosis of tuberculosis had previously been made in 26, although no conclusive evidence of tuberculosis had ever been found. In 35, foci of infection were discovered and in all the foci were removed. However, the fever did not subside in a proportionately larger number of these than in the group without focal infection. The investigation of the subsequent histories revealed that in 55 the fever finally disappeared after a period of from one month to six years after leaving the Clinic. Thirty-eight patients had continued to have fever. Seven had died. Three came to autopsy which disclosed that one had died of streptococcus septicemia, one of bacterial endocarditis, one of sarcoma of the kidney; in one a mass had been discovered in the abdomen before death; in the remaining three no cause of death could be assigned.

In considering the diagnosis of obscure fever it is convenient to divide the cases into two groups. This is done not only because it facilitates discussion but, what is more important still, because it separates two different clinical problems. The first group comprises cases with low-grade fever, the temperature only occasionally exceeding 100° and rarely reaching 101°F. The symptoms are not severe and the patients are usually ambulant. The second group comprises cases with higher fever and symptoms which are usually incapacitating. The patients as a rule are confined to bed.

GROUP I. LONG-CONTINUED, LOW-GRADE FEVER

Every physician is familiar with the difficult problem these patients present. They come to consult him complaining of weakness and lassitude, of lack of energy and endurance. All the zest for life has

gone, they must whip themselves to undertake tasks which formerly they performed lightly and when the tasks are done, they are exhausted. Some have headaches, others digestive symptoms, still others complain of palpitation of the heart and discomfort over the precordium. All are ill at ease, apprehensive, vaguely nervous, both mentally and physically depressed. Usually they have already consulted many physicians and almost as many different diagnoses have been made. Often they have been put through more or less exacting therapeutic procedures; teeth have been extracted, tonsils removed, sinuses opened, the appendix excised, the gall-bladder drained, the tubes taken out, the ureters dilated, the pelvis of the kidney washed, and some have spent long months, even years, in tuberculosis sanitaria; and yet they feel no better and the fever persists. What can be wrong with these recalcitrant patients who firmly resist the persuasive influence of all our harsh as well as our gentle methods of treatment? If we follow them over a long period of time we discover that finally they group themselves into three classes:

1. In a certain number, about 40 per cent, characteristic signs and symptoms develop which permit us, at last, to make an accurate diagnosis.

2. In another group, about 50 per cent, the symptoms slowly disappear, the fever subsides and the patients get well, although we are never able to arrive at a well-supported diagnosis.

3. In yet another group, about 10 per cent, the symptoms and the fever persist for many years and in spite of the most careful observation and painstaking examinations no satisfactory diagnosis is ever reached.

Here we shall pause to emphasize an important matter, no doubt tacitly understood, and yet we speak of it in order to avoid the slightest misunderstanding. Let it be assumed that the patients we are now discussing have all been thoroughly and intelligently studied and that every possible aid to diagnosis has been exhausted. We are not here in the least concerned with diagnostic failures due to lack of ordinary skill or of ordinary diligence.

Patients upon whom an accurate diagnosis is finally made. In the group of 36 patients with long-continued, low-grade fever who have come under our care an accurate diagnosis finally has been made

upon ten. Upon six others a presumptive clinical diagnosis was made, but its correctness may well be questioned.

The 10 accurate diagnoses were as follows:

Malta fever	3
Pulmonary tuberculosis	2
Hypernephroma	2
Hodgkin's disease	1
Ureteral stricture	1
Tertiary syphilis	1

The 6 questionable diagnoses were as follows:

Tuberculosis—pulmonary	1
Tuberculosis—mesenteric glands	1
Tuberculosis—perirectal abscess	1
Rheumatic fever	1
Malta fever	1
Multiple myeloma	1

As an illustration of obscure fever at last correctly diagnosed we cite the following case:

Case 1. V. B. A married woman, 32 years of age, was referred to us for examination by Dr. E. H. Richardson, September 9, 1925, on account of long-continued, unexplained fever. As a child the patient had been delicate and had suffered constantly from indigestion. She was a frail woman when she married at twenty years of age. Shortly after marriage she moved to the country where her husband conducted a dairy farm. She became interested in all the farming activities, lived much out of doors, began to gain in weight and strength, and soon was a robust, healthy woman. In 1921 dilatation and curettage of the uterus had been performed because she had become increasingly concerned over not becoming pregnant. Menstruation had always been somewhat painful, but after the operation the pain was less severe. In 1923 a Rubin test had been made by Dr. Richardson without fruitful results. In January 1924 she grew unaccountably nervous. She had always been high-strung and restless but this nervousness was different from anything she had felt before. She became agitated and tense; there were periods of depression and unprovoked spells of weeping accompanied by palpitation of the heart. She felt utterly wretched and good for nothing. An examination by her physician disclosed no abnormality. During the following summer and autumn she was somewhat better but still miserable, always tired and exhausted by the least effort. In February 1925 she had an attack of fainting and her temperature taken on that occasion registered 102°F. This led to further observation which revealed that each day there was a little fever. In March she was thoroughly examined at the University Hospital, Charlottesville, under the

direction of Dr. J. C. Flippin. No single abnormality was discovered. During the summer again she was a little better but always tired and ill at ease. The temperature rose a little each afternoon, the rise being especially noticeable after any exertion. An infected tooth was extracted, but this had no effect upon her condition. At the end of August the patient spent another period in the hospital during which a second complete medical review was conducted, again with a negative result. She was convinced that the fever and ill health were due to some pelvic disorder. She had had leukorrhea constantly and pain in the lower abdomen, in the back and down the right leg. Furthermore, menstruation had become scanty and on those occasions when the flow was freer than usual she had felt better. She was convinced from her own observations that her temperature went higher after work requiring constant stooping than it did after an equal amount of exertion carried out while standing. For these reasons she once more consulted Dr. Richardson. Dr. Richardson was not able to find the slightest evidence of disease of the pelvic organs and invited us to investigate the situation.

Examination. Temperature, 99.4°; pulse, 96; respirations, 16; blood pressure, systolic 116, diastolic 70; weight, 128 lbs.; height, 5 ft. 3 in.

The patient was a well nourished woman, about the average weight for her height and age. Her color was good and she had the appearance of vigorous health. The eyes were normally prominent, the extra-ocular movements normally executed. The pupils were equal and reacted actively to light and on accommodation. The teeth were in good condition but the gums were red and a little swollen. The pharynx showed nothing remarkable. There was no enlargement of any of the superficial lymph nodes. The thyroid was of average size, symmetrical. The chest was well formed and symmetrical, the costal angle about 100°. The lungs were quite clear. The apex beat of the heart was in the fifth intercostal space well within the nipple line. The sounds were clear and of normal quality. The abdomen was normal in appearance; the walls soft and relaxed. There was a little tenderness on deep pressure over the right lower quadrant. The liver and spleen were not enlarged. The extremities showed no gross arthritic changes. The reflexes were normally active.

Since the patient had been examined so recently and thoroughly under the competent care of Dr. Flippin, we deemed it quite unnecessary to repeat the many tests and special examinations which had been made. The impression left by a careful weighing of all the facts before us is clearly expressed by a brief quotation from a letter written immediately after the patient's visit. "We are unable to find any concrete abnormality and can give no explanation for the symptoms from which Mrs. B. suffers. She remains convinced that there must be some disorder in the lower abdomen which is responsible for her ill health. However, neither Dr. Richardson nor ourselves can find any evidence of it. In view of the fact that there is no clear explanation for the symptoms we suggested to Mrs. B. that she take a long period of complete rest. By resting sporadically during the past year and a half she has gotten nowhere. It is possible that whatever is wrong may somehow adjust itself if she goes to bed for six or eight weeks and then gradually begins to get up and about."

The patient returned home and began at once to follow the suggestion that she take a prolonged rest. However, little if any improvement followed. She became more and more nervous and restless and at the end of six weeks was almost frantic. Again elaborate series of examinations were made. The constant abdominal discomfort brought up the questions of appendicitis and cholecystitis and the prospect of operation was discussed but wisely abandoned. The roentgenogram showed mild arthritic changes in the lumbar spine and the patient was given a support to wear. The support relieved the pain in the abdomen and back and from then on she was more comfortable. However, nervousness and slight fever persisted, but these also diminished and after some months disappeared. At a visit in May 1926 the patient reported that she was feeling much better and that she no longer had fever.

Under date of November 27, 1927, the patient answered a note of inquiry about her progress as follows: "I am feeling splendidly, better than for the past three years. Never have spells of fatigue or nervousness or fever. As long as I wear a sacro-iliac belt I can work my flower garden from two to six hours a day without any discomfort. Knowing that nervous diseases and infections can be aggravated by a sprain of the sacro-iliac joint and that proper support relieves the suffering I have always wondered what caused my fever and all the other symptoms which came with it. I had the most thorough examinations and tests ever given and since no cause could be found for my symptoms I was called neurotic. I still get furious at the word 'neurotic' for I feel sure there was a cause for my sickness but until a few weeks ago I had no idea what it could be.

"The dairymen of the county entertained the Medical Society and Dr. Harding of Detroit spoke on Milk and its Relation to Disease. Dr. Harding has made a study of this subject and in the course of his talk told of the transmitting of the germ of contagious abortion, from the cow through the milk to humans, and gave this as the cause of many heretofore unexplained fevers, which lasted as long as six months, as well as the cause of a type of miscarriage and other pelvic troubles.

"It seemed apparent that my sickness could be traced to this cause, as we have a herd of registered Holsteins, infected for years with contagious abortion of the most virulent type. The milk sold from our dairy is pasteurized in Charlottesville before being distributed, but raw milk is used at home. I am anxious to know if any studies along this line have been made at Hopkins and if an agglutination test would still detect the presence of the abortion germ in my blood stream. Any information you can give me will be gratefully appreciated."

This letter was a violent jar to our stupidity. As soon as the suggestion was made it seemed quite evident that the patient had had Malta fever. The observations of Keefer published in 1924 were the first definitely to establish the existence of infection with Brucella abortus as a clinical entity. When the patient consulted us in 1925 we had not had any personal experience with the disease, but during 1926 had identified by means of the agglutination test two puzzling instances of prolonged, unexplained fever as cases of Brucella abortus infection. Therefore, when the patient's solution of the mystery of her illness was flashed upon us, we were prepared to see its complete reasonableness. Tests of the serum

in a number of laboratories showed strong agglutination of Brucella abortus in dilutions up to 1 in 80.

Patients who recover without a satisfactory diagnosis being made. In our group of thirty-six patients with long-continued, low-grade fever, seventeen recovered although a satisfactory diagnosis was never made. An illustrative case is the following:

Case 2. J. F. A young married woman, 23 years of age, was referred to us for examination on August 7, 1924, by Dr. E. P. Gray, complaining of fever, loss of strength and endurance, and shortness of breath. Her illness had begun in April 1924. During the previous summer and winter she had felt quite well except that occasionally she had had a little pain in the right lower quadrant of the abdomen. In May this pain became more pronounced; the diagnosis of appendicitis was made and the appendix was removed. As she convalesced from the operation, it was noticed that she had a little fever. The temperature rose to about 99.5° each afternoon. At the end of three weeks the temperature came to normal. She left the hospital and no further observations on the temperature were made. About the beginning of June she was still feeling languid and good for nothing. Her temperature was again taken and it was found that each afternoon it rose to a point between 99° and 100°, averaging about 99.6°. At this time the patient was feeling distinctly below par. She had no energy and the least exertion exhausted her. A period of rest in bed was tried and then a stay of a week or two in the mountains without any improvement in her general condition and without any effect upon the fever. In addition to being exhausted, any effort made the patient very short of breath and brought on palpitation of the heart.

The patient had never been robust but previous to this illness she had been well. She had had a number of the usual childhood infections and at twelve years of age typhoid fever. The tonsils had been removed when she was seventeen years old. Before their removal she had had many attacks of tonsillitis. In July 1924 the teeth were carefully investigated and three infected ones were extracted without any improvement of her general symptoms and without reduction of the fever. There had been no cough and no important digestive symptoms except pain and discomfort in the lower part of the abdomen. At the time of the appendectomy a pelvic examination had been made but no disorder in the pelvis had been discovered. There had been no arthritic manifestations. The patient's weight previous to her illness had averaged about 135 pounds. Following the operation she lost twenty pounds but she slowly regained ten pounds.

Examination. Temperature, 100°; pulse, 120; respirations, 26; blood pressure, systolic 114, diastolic 58.

The patient was sparely nourished, ten pounds below the average weight for her height and age. The skin was a little pale; the mucous membranes had a better color. The eyes were normally prominent. The pupils were equal, regu-

lar, reacted actively. The eye movements were normal. The fundi showed no abnormality. The teeth were in good condition. The tongue was clean. The pharynx showed no abnormality. The tonsils had been completely removed. No enlargement of any of the superficial lymph nodes. The thyroid was barely felt, symmetrical, with no nodules. The chest was long and thin with a narrow costal angle. It was symmetrical. Movements equal on the two sides. The lungs were quite clear. The apex beat of the heart was in the fifth interspace inside the nipple line. The area of cardiac dulness was not enlarged. The heart sounds were clear and of normal quality. The pulse was regular but rapid throughout the period of the examination. The peripheral vessels were not thickened. The abdomen was markedly enteroptotic in conformation. Along the right border of the rectus from the umbilicus nearly to the symphysis was the scar of the recent operation wound. The abdominal wall was everywhere soft and relaxed. There was no tenderness. No masses could be felt. The liver and spleen were not enlarged. The right kidney was easily felt; it was smooth, freely movable, not tender. The extremities showed no arthritic manifestations. The deep reflexes were normally active.

Laboratory examinations. Blood count: Hbg. 78%; red blood cells 4,064,000; white blood cells 7,280. Wassermann reaction on the blood serum negative. Urine: Contained a trace of albumin and in the sediment there were many pus cells and a few red blood corpuscles. Gastric contents: Showed free HCl 18. Total acidity 40. Stool: Showed no abnormality. Test for occult blood was negative. Intracutaneous tuberculin test was negative in a dilution of 1:10,000. Basal metabolic rate: +3.5%.

Laryngological examination: No evidence of infection in the nose, throat or ears.

Roentgenograms: Chest: A slight amount of fibroid infiltration of both lungs which is limited to the hila, the peripheral zones and apices being clear. Kidneys and bladder normal. No evidence of stone.

Evidently, then, the examination was quite negative in every way except for the presence of a slight degree of anemia and a little pus and blood in the urine. At the patient's home further studies of the urinary tract were made and the right ureter was catheterized. The urinary findings were clear and there was no evidence of infection in the urinary tract.

With rest the patient improved somewhat, but the elevation of the temperature persisted and gradually she developed an increasing amount of pain in the lower abdomen with nausea and frequent vomiting. From February 5, 1925, to April 1, 1925, the patient was in the Johns Hopkins Hospital under the care of Dr. W. S. Thayer. Again an unusually exhaustive investigation was made, but no abnormality whatsoever was discovered except a slight degree of secondary anemia. On admission the patient weighed 112 pounds; on discharge her weight had risen to 120 pounds. There was improvement in her general condition but throughout the stay in the hospital the temperature was constantly somewhat elevated. In the morning it was between 97° and 98°. In the evening it rose to between

99.4° and 100°. From this time on she gradually improved and at some subsequent period the fever completely disappeared. A letter dated September 18, 1926, states that the patient at that time was perfectly well and was enjoying the best health that she had had for the previous three years. Subsequent reports from her indicate that she has remained perfectly well.

Patients who continue to have fever for many years and no satisfactory diagnosis is ever reached. In our group of thirty-six patients with long-continued, low-grade fever, three continued to have symptoms for from three to thirty years. The following story of one of these patients well illustrates the condition:

Case 3. E. B. In 1908 we examined a graduate nurse, 33 years of age, who was complaining of cough, loss of weight and hemoptysis. She had never been a very robust woman and had always been subject to winter colds and bronchitis. In 1901, after a period of nervous strain, she had had an attack of unconsciousness lasting about twenty-four hours. During the following two years she had had repeated attacks of fainting. From then on the attacks had come only at very long intervals. The examination revealed a little dulness and harsh breathing at the left apex. A diagnosis of pulmonary tuberculosis was made and the patient spent nearly a year at Trudeau Sanatorium. While there, she was in bed almost constantly and yet throughout this period her temperature each day rose to the neighborhood of 100°. After returning from the sanatorium the patient was no better. Her fever continued and the pulse rate was often rapid. For short periods the pulse rate would rise to 160 beats to the minute and at these times there was shortness of breath and cyanosis. The tonsils were removed without any benefit. The nervousness, the fever, the tachycardia all suggested thyroid disease and in February 1910 the right lobe of the thyroid gland was excised by Dr. Richard H. Follis at the Johns Hopkins Hospital. Following this operation there was very little improvement. For a while the patient was somewhat stronger but she continued to be quite nervous, had a rapid pulse and recurring bouts of palpitation and tachycardia. Her digestion was poor and there were frequent attacks of diarrhea. The temperature continued to range between 98° and 100° and the pulse rate from 80 to 120. Late in 1911 there was a recurrence of the attacks of fainting. The periods of tachycardia became more frequent and during these attacks there was a great deal of oppression over the heart and sometimes pain running down the inner side of the left arm to the wrist. The hands and feet constantly were cold and blue. Nitroglycerin taken in the attacks seemed to give some relief. In February 1912 the patient was operated upon again and the left lobe of the thyroid removed. Throughout the period of her stay in the hospital the temperature oscillated between 98° and 100°.

During the following two years the patient's condition gradually improved somewhat; at least the attacks of palpitation became less frequent and less severe.

However, digestive symptoms were very prominent, lack of appetite, gas, pain in the abdomen and later nausea and vomiting. Throughout this period the temperature showed a daily elevation, going each afternoon to a point from 99.6° to 100°. Frequent examinations made during this period were always negative except for some slight signs at the apex of the left lung. In March 1915 the patient was again in the Johns Hopkins Hospital, on this occasion complaining of digestive disturbances and of the attacks of palpitation with pain over the heart radiating down the left arm. The physical examination and all of the laboratory examinations were quite negative except that there were many extrasystoles. The blood pressure was observed during one of the attacks of palpitation with pain. At the beginning of the attack the systolic pressure was 118; during the attack it rose to 150.

During the following five years the patient was seen frequently on account of digestive disturbances, attacks of palpitation, weakness and an almost constant slight elevation of temperature. She was able to work but it required great fortitude for her to carry on. The physical examination was always negative except for tachycardia. The blood pressure was within the limits of normal. In 1920 she was in the Johns Hopkins Hospital again for a period of rest. Her main complaint at this time was that she was very weak and felt generally miserable. During her stay in the hospital the temperature varied from 97° to 99.6°. From 1920 to 1925 the digestive difficulties were in the foreground. She had almost constant nausea and from time to time vomiting, and always discomfort and frequently actual pain in the abdomen. The symptoms suggested the possibility of peptic ulcer but all of the examinations were quite negative.

In January 1925 the patient spent two weeks in the Union Memorial Hospital. At this time the digestive symptoms were particularly annoying. There was constant pain in the epigastrium, inability to eat, nausea and frequent vomiting. After a prolonged period of rest these symptoms were somewhat better and she was able to return to work. Her weight at this time had fallen from the high point of 145 pounds to 124 pounds. During this stay in the hospital there was very little fever, the temperature only occasionally going to 99.6°. In 1926 the patient fell and fractured her left hip. When the fracture healed, there was ankylosis at the hip-joint. During the early autumn of 1928 there were again very severe digestive symptoms which made the patient constantly miserable. There was constant abdominal pain, often radiating to the right shoulder, and there was the unpleasant sensation of some difficulty in food passing down the gullet. Again the examination was quite negative excepting that it was noted for the first time that the blood pressure was a little elevated, namely, systolic 156, diastolic 88.

In November 1930 the patient came for examination complaining of severe pain in the leg and digestive difficulties. There was an absolute distaste for food, almost constant nausea, frequent pain in the abdomen and waves of weakness and faintness. She had fought valiantly to get her weight up to 140 pounds, but

in a few months it had fallen off again to 115 pounds. Except for the ankylosed hip, the result of the old fracture, and evidence of a mild chronic arthritis, the physical examination revealed no abnormality. During the previous five years the patient had lost interest in her temperature and had made only occasional observations. When the temperature was taken in the late afternoon it was nearly always a little elevated. It was not unusual to find it at 100°. At this examination the blood pressure was a little more elevated, namely, systolic 168, diastolic 80.

During the past five years there has been no essential change in the patient's condition.

This is a remarkable instance of fever lasting almost continuously over a period of twenty-five years. At first it was thought that the fever and other symptoms were associated with a mild tuberculous infection. The evidence of the infection was very slight indeed and after twenty-five years of almost continuous observation I think it is safe to say that the patient never had an active tuberculous infection to account for her illness. In view of the peculiar vascular manifestations, a diagnosis of hyperthyroidism was made. The removal of chronically infected tonsils had no effect whatsoever upon the patient's symptoms. Following partial thyroidectomy there was only temporary, and by no means striking, improvement. The remaining lobe of the thyroid was then removed with equally disappointing results. Later the vascular symptoms were less pronounced and digestive disturbances came to the fore. On repeated examination no organic disease was ever found to explain these symptoms. In a word, no satisfactory diagnosis of the patient's illness or of the cause of her symptoms has ever been reached in spite of careful and frequently repeated investigations.

What, we should like to know, was the cause of the fever in the large group of patients upon whom we could make no satisfactory diagnosis? Perhaps it is useless to speculate and yet speculation is warmly invited. In a large number tuberculosis was suspected and at one time or another this diagnosis was made in nearly all. In another group foci of septic infection were assumed to be present and to account for the fever, but the effect of removing these foci of infection was in most instances singularly disappointing. Without being able accurately to determine the cause of the fever in any specific case, we may conclude that it must have been due to:

1. Some mild specific infection, *e.g.*, tuberculosis, Malta fever, rheumatism, or
2. Some focus of septic infection, *e.g.*, tonsillitis, appendicitis, pyelitis, or
3. Uncertain causes about which we are only meagerly instructed, *e.g.*, metabolic disorders, neurogenic fever.

1. Specific infections

Tuberculosis. We have said that tuberculosis was suspected in all. Tuberculosis more frequently than any other of the chronic infections causes a slight, long-continued fever. Indeed such a slight fever is a characteristic, almost distinctive, feature of the disease. In addition to this the patients complained of the very symptoms which are precisely those usually complained of by the tuberculous, namely, weakness, fatigue, lack of endurance, tachycardia, sweating and so on. Furthermore, all physicians know that often it is very difficult to discover the location of a tuberculous lesion which may be causing these general symptoms. Therefore, it is not at all surprising that under these circumstances tuberculosis was always suspected, nor is it in any way remarkable that very often this diagnosis was made. And yet in not a single instance was the diagnosis securely established. We have had the opportunity to observe some of these patients at intervals over many years; others have spent long periods at tuberculosis sanatoria and resorts. Opinions about them differ; some physicians are convinced they have tuberculosis, others are equally sure they have not. The conclusive evidence, namely, the demonstration of tubercle bacilli, has never been furnished. In the light of this experience we are prepared to defend the statement that, whereas tuberculosis is the most common cause of long-continued slight fever, it is seldom the cause of ***unexplained***, long-continued, slight fever.

When a patient with low fever comes for examination complaining of general malaise, weakness, exhaustion and tachycardia, the physician at once makes a tentative diagnosis of tuberculosis. With this possibility foremost in mind the examination is planned especially to disclose the location of the tuberculous lesion. It is searched for carefully and assiduously, and if the search be thorough and often repeated, the tuberculous lesion seldom escapes detection. However, now and again it is overlooked and the memory of these unfortunate occasions is so bitter and tenacious that the physician is apt to diagnose tuberculosis whenever he is unable to discover any other satisfactory explanation for the symptoms. We all recall these sad experiences. Slight fever, slight constitutional symptoms, negative examinations, negative roentgenograms; later, an attack of pleurisy with effusion, a manifest pulmonary tuberculosis, tuberculosis of the pelvic organs, tuberculosis of the mediastinal or mesenteric glands, etc.

No one faces lightly the possibility of a repetition of these errors and therefore perhaps we are apt to be too cautious. When all has been said, we must allow that it is as grave an error to diagnose tuberculosis when it does not exist as it is to miss it when it is present. It is right and proper that tuberculosis should always be suspected as the cause of unexplained fever and the suspicion tenaciously held until some other cause for the fever is discovered. However, the diagnosis should never definitely be made upon circumstantial evidence alone.

In this connection we wish to say a last word by again calling attention to a valuable test which is too often neglected, namely, the tuberculin test. The intracutaneous tuberculin test is easy to perform and utterly dependable in the information it gives. A reaction indicates tuberculous infection, not tuberculous disease, and therefore is of little value in diagnosis. But a failure to react indicates, aside from a few well-known exceptions, the absence of tuberculous infection and this information may be of the greatest value in diagnosis. From 60 to 70 per cent of all adults will react to the intracutaneous tuberculin test with a dilution of 1 to 1000, but among those who fail to react there will be many who at one time or another may have symptoms which arouse a suspicion of the presence of tuberculosis. Under these circumstances to demonstrate that the patients are insensitive to tuberculin will definitely and at once dispel the suspicion. To illustrate how precisely at times the test may guide diagnosis we recall an experience published some years ago (4).

In the spring of 1919, during the wane of the influenza epidemic, we were consulted by two young women, one within a few days of the other. Both gave similar histories, a fairly acute onset of the illness characterized by cough, sputum, loss of weight and strength and a little fever. Both showed a small area of consolidation in an upper lobe. The diagnosis lay between a patch of unresolved pneumonia and tuberculosis. One reacted to the intracutaneous tuberculin test whereas the other showed no sensitiveness to tuberculin even when a 1:100 dilution was injected into the skin. It was our opinion that neither was tuberculous, but the one we felt confident we could dismiss without concern, the other we held under careful supervision. The patient who failed to react to tuberculin made a prompt and lasting recovery; the other patient failed to improve and a few months later tubercle bacilli appeared in the sputum.

Malta fever. When the identity of a disease previously unrecognized is at last securely established, we wonder what physicians may have called the disorder before they had learned to know its characteristic features. There can be little doubt that for a long time Malta fever has been a prevalent infection in the United States, even though it has been recognized as a widespread and common disease only during the past decade. Our own experience with it makes us surmise that heretofore it has often been masked as an obscure fever. It would be difficult to conceive of a disease more cunningly devised to confuse diagnosis. The symptoms are usually mild and undistinctive; they are continued over a long period of time and both the physical examination and the results of laboratory tests are conspicuously uninforming. It is only after we have become acquainted with the clinical features of the disease that we grow to suspect its presence and then use the specific biological tests, *i.e.*, cultivation of the Bacillus melitensis and the serum agglutination reaction, to confirm the suspicion. Since we have learned in this way to discover the infection we have identified it in ten or more patients who formerly would have been classed under diagnostic puzzles and as sufferers from an unexplained fever.

Rheumatic fever. We are all familiar with the mild constitutional symptoms that often accompany a rheumatic infection which, nevertheless, may cause a crippling valvular disease of the heart. Unfortunately, to recognize the disease we must still depend solely upon clinical manifestations and when these manifestations are mild, they may consist chiefly of a low, long-continued fever. It is unnecessary to dwell upon the difficulty of detecting an early rheumatic affection of the heart valves, especially of the mitral, which are also the ones most often involved. Fortunately, for the purpose of diagnosis the heart muscle as well is frequently attacked by the infection and the changes there produced may cause betraying alterations in the electrocardiogram. More than once have we seen children vaguely ill with a continuous slight fever in whom the only diagnostic clue was a disturbance of the form and rhythm of the deflections of the electrocardiogram. Under these circumstances the presence of rheumatic fever as the cause of the symptoms is probable to a high degree. In the group of cases we have gathered together rheumatic fever appears but once,

and even then only as a probable diagnosis. We believe that this figure does not at all represent its real importance in this connection, for again and again we have observed circumstances under which rheumatic fever seemed the only reasonable diagnosis to make and yet, because it was impossible to follow the patient after discharge from the hospital, the diagnosis was never definitely established. We are convinced that if we had the opportunity for prolonged observation, many children with unexplained fever would later develop the unmistakable signs of valvular heart disease. The studies of Alt and Baker demonstrate this to be true and the high incidence of rheumatic fever as a cause of unexplained fever in the group of patients they observed is, we do not doubt, more nearly correct than the low incidence our figures suggest.

2. Pyogenic infections

The impression has strongly prevailed that obscure fever is commonly due to hidden foci of infection. This opinion has been fostered by the preoccupation of physicians with focal infection, a conception which has dominated medical practice during the last quarter of a century. Never before, at least not in modern times, has a theory of disease so completely captured the imagination of the profession and been so enthusiastically followed in practice. The theory is extraordinarily beguiling, because it explains simply and directly many of the most obstruse and bewildering problems in pathogenesis and still more so because it offers an equally simple and direct rule of practice. No patient can feel that he is neglected while his body and mind are being scrutinized thoroughly and the searching tests of science applied with meticulous care to every function. Nor need any physician be oppressed by the sense of fruitless inactivity so long as there are teeth to be pulled, tonsils to be enucleated, sinuses to be reamed, thyroids to be excised, gallbladders to be drained, appendices to be removed and kidneys to be probed. For a period, the practice of medicine became almost solely a routine search for foci of infection and the practice of surgery a routine removal of the foci found or suspected. Science was rampant, for the simplest medical observation had become an "investigation" and the usual examination a "systematic study." Those were glorious and profitable years, cut short, alas, by the onset of the financial depression!

If we consider the relation of long-continued, unexplained, low-grade fever to focal infection we must conclude from experience that there is no well-established relation between them. Occasionally we observe that fever subsides after foci of infection are eradicated, but this happens so infrequently that we are justified in asking if the result may not be a coincidence rather than the effect of the operation. When we examine large numbers of cases, for instance, the series published by Kintner and Rowntree, the results certainly justify this sceptical attitude, and our own experience, though less extensive, has confirmed us in the belief that long-continued fever is rarely caused by hidden foci of infection. To prevent misunderstanding we should make clear precisely what is meant by "hidden foci of infection." It must be apparent that we do not mean extensive areas of infection, for instance, empyema, acute appendicitis, acute suppurative cholecystitis, pelvic abscess, and so on. These are indeed the best illustrations one could find of foci of infection, but the recent use of the term has restricted it to designate localized areas of chronic infection usually without suppuration, as illustrated, for instance, by chronic tonsillitis, chronic sinusitis, infection about the roots of teeth, chronic cholecystitis, etc. This restricted use of the term is similar to the way in which we employ the term "infectious arthritis," that is, to exclude arthritis of known etiology, which is of course the truest form of infectious arthritis. We may briefly review our experience with the more common types of focal infection.

In but a single instance have we observed a low-grade fever to subside following the extraction of an infected tooth. We are well aware of the many examples reported in print and by mouth in which fever has disappeared after the removal of teeth. We have no desire to discredit these observations but wish merely to record that our experience has been less fortunate.

Tonsillectomy and adenoidectomy are sometimes followed by the disappearance of slight fever in young children, but only very rarely in adults. The draining of infected sinuses perhaps somewhat more often.

Chronic bronchitis and chronic nontuberculous basilar lung infections are frequently accompanied by a low-grade fever, but the symptoms and signs of these conditions are usually apparent and therefore they may not be classed as causes of unexplained fever.

The diagnosis of chronic appendicitis as an explanation for vague digestive symptoms often associated with low-grade fever is rapidly falling into disuse. We no longer recognize as a clinical entity a continuous inflammation of the appendix capable of producing these symptoms and a febrile reaction. Recurring appendicitis and the mechanical effects following previous attacks of appendicitis give entirely different clinical manifestations. Nevertheless, owing to the fact that many patients with long-continued, low-grade fever complain bitterly of digestive symptoms, appendectomy is a popular method of treatment. Never have we seen appendectomy permanently relieve the symptoms nor abate the fever.

Since the diagnosis of *chronic appendicitis* slowly has been abandoned as a satisfactory explanation for vague abdominal symptoms the diagnosis of *chronic cholecystitis* or, as it is often put, *the chronic gallbladder* gradually has been brought forward to replace it. The meaning of this diagnosis lacks precision, which is probably an advantage, since the symptoms it connotes are themselves vague and of uncertain origin. We shall not attempt the difficult task of defining it, nor is it our desire to justify its use. We wish merely to point out that the present tendency to ascribe vague abdominal symptoms to chronic infection of the gallbladder leads usually to therapeutic disappointment (5), and especially is this true when we anticipate that removal of the gallbladder will abolish a long-continued, low-grade fever, unless the accompanying symptoms point clearly and unmistakably to gallbladder disease. This they seldom do; in our own experience never, for the two occasions upon which patients with prolonged, unexplained fever were operated upon and the gallbladder excised there was no convincing pathological evidence of disease of the gallbladder, and the patients were not benefited.

Infection in the urinary tract is a common cause of long-continued fever, but if this fact is remembered and the urine carefully examined the infection seldom escapes detection. It should be needless to comment upon the necessity of examining catheterized specimens, especially in women, and yet the error is frequently made of concluding from the presence of pus in voided specimens that there is infection in the urinary tract. It is equally important that cultures be made

of the urine, for infection may exist even though only a few pus cells are seen in the sediment.

3. Uncertain causes

It is with reluctance that we now turn to consider the possibility of nervous influences and metabolic disturbances being the cause of long-continued, low-grade fever. Here we meet with little that is precise and firmly established and yet there are many observations, some of them from almost daily clinical experience, which suggest that these factors may at times play an important rôle in the production of fever. About one of them at least we are now fully informed and it is one which has an important bearing upon practice. We refer to the loss of the heat-dissipating mechanism of sweating. Woodyatt (6) has recently called attention to this in a dramatic way. He had an opportunity to study very thoroughly a young woman with unexplained fever and distressing constitutional symptoms of a character commonly referred to as functional or psychoneurotic. The symptoms had come on shortly after moving to the South. At the end of the period of observation no plausible explanation for the fever had been discovered. Aid was sought from eminent consultants, but they could suggest no satisfactory diagnosis. All had noticed that the patient was afflicted with ichthyosis but none had paused to consider this as a possible explanation for the symptoms until the happy inspiration occurred to Woodyatt. As a result of the ichthyosis there was complete suppression of sweating and when the surrounding temperature was high the body, deprived of this regulating mechanism, stored heat, whereas with the surrounding temperature low, the other mechanisms for heat dissipation were sufficient to keep the body temperature at a normal level.

Fever is commonly associated with disturbed function of the thyroid gland and of the ovaries. With hyperthyroidism the temperature is nearly always elevated, the fever seemingly being due to the increased heat production. However, occasionally there is a little fever with hypothyroidism. Lee (7) has reported an instance of mild hypothyroidism without myxedema accompanied by fever which disappeared when small doses of thyroid were given, and which reappeared when-

ever the thyroid was withheld. At the present day the diagnosis of thyroid disorders is so well established that cases of this condition are seldom misinterpreted. Therefore, they are no longer a cause of *unexplained* fever. Nevertheless, in doubtful situations it is well to bear the possibility in mind and to prove it with suitable investigations.

It is common knowledge that menstruation is frequently accompanied by a little elevation of the temperature. This occurs even in healthy women as is shown, for instance, by the careful observations of Griffith and others (8). When there is present some slight infection, the influence of menstruation upon the body temperature may become more pronounced. This is observed conspicuously during the course of chronic pulmonary tuberculosis (9). It is not uncommon to see charts of the temperature of tuberculous women that show regularly an elevation at the menstrual period, although there may be no fever at other times. These facts are recalled not to furnish evidence that the activity of the ductless glands is the cause of long-continued fever, but merely to suggest that possibly it may be. The matter is altogether too uncertain to be of any clinical value at the present time.

There can be no doubt whatsoever that nervous and emotional influences have an effect upon the body temperature. Even in perfect health a transport of anger or of joy may raise it. It is characteristic of these reactions that they are brief, for the temperature soon sinks to normal. The effects are greatly exaggerated in patients harboring an infection which of itself often produces fever. This occurs commonly in patients recovering from the symptoms of pulmonary tuberculosis. Even though for weeks the temperature may have been at a normal level, any excitement, a visit from a friend, a game of cards, may be followed by a febrile reaction lasting for hours. The interesting question to ask is whether nervous strain or emotional tension sustained indefinitely at a lower level of stimulation can produce a slight, long-continued fever? The possibility is attractive, for were it well founded, it would give a satisfactory explanation for the many instances of fever in patients who finally recover, although in spite of exhaustive examinations they remain undiagnosed. Moreover, most of these patients complain of just those vague symptoms which are characteristic of psychoneurotic states. At the present time we can give no precise answer to this important question. Certainly

we cannot deny the possibility that nervous states may cause a steady long-continued fever, and yet to accept this explanation for any particular instance exposes us to the gravest clinical risk. Very often we encounter circumstances which seem to justify the diagnosis of neurogenic fever and yet a little later some other adequate explanation for the fever is discovered. I need merely recall the patient, already referred to, who was studied by Woodyatt. No doubt the correct attitude for the physician—certainly the safe one—is to admit the general possibility of neurogenic fever and yet never to venture to make this diagnosis.

In support of the possibility we may list briefly the following observations (10):

1. There can be little doubt that hysterical manifestations may be accompanied by fever. Usually the fever is of short duration, but it may last for days and even longer. Sometimes it can be controlled by hypnosis.

2. In psychotic patients, whether agitated or depressed, a little fever is almost regularly observed in spite of the fact that careful examination reveals no cause for its occurrence other than the abnormal mental state.

3. Psychiatrists have often commented upon variations in the temperature of psychoneurotic patients regularly recurring in relation to psychiatric treatment and mental trauma.

4. That obscure clinical condition called *effort syndrome*, exhaustion syndrome, disordered action of the heart or neurocirculatory asthenia is nearly always accompanied by slight fever. The fever may persist for years and the most thorough investigation fail to discover any acceptable cause for it. The character of the symptoms and their long duration force us to look upon effort syndrome as a neurosis of obscure mechanism and origin. Unexplained, slight fever is so frequently present in this condition that we regard it as an important element of the clinical manifestations.

Finally, we must at least notice the possibility, frequently suggested, that some persons may have a thermoregulatory mechanism set at a high level and for them a temperature between 99° and 100° may be normal. The suggestion is enticing, for it would be a great comfort, when harassed by doubt and uncertainty, to seek refuge in that reas-

suring conviction. Whether or not actually at times this may be the case, we cannot decide, but if it happens at all, it must happen very seldom, as is clearly demonstrated by the routine observation of the temperature of patients upon hospital wards. However, the question has little practical significance, no matter how interesting and important otherwise it may be. Even though the physician be convinced that such anomalies do sometimes occur, he is never justified in making this diagnosis under any concrete circumstances.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Body Water. The Exchange of Fluids in Man. By JOHN P. PETERS. 1935. 405 pp. $4.00. (*Chas. C. Thomas, Springfield, Ill. and Baltimore, Md.*)

This book is chiefly a critical discussion of fluid exchange in the body and of the theories which have been advanced to explain the observed phenomena. The compilation of a great deal of information and a very useful bibliography add to the value of the treatise. There is little evidence that the author has attempted to over-simplify complex problems in order to please the general reader. He has, rather, endeavored to present existing problems in their true complexity and to give a critical survey of the evidence for the various explanatory theories.

In this volume all the major types of fluid exchange are discussed in some detail: water intake and water loss, the formation and movement of lymph, the exchanges between tissue cells and interstitial fluids, fluid transfers between blood cells and serum, etc. The book should be of great value to those interested in kidney function, alimentary exchanges, and all kindred processes involving the movements of fluids within the body.

C. McC. B.

Genetics and the Social Order. By MARK GRAUBARD. 1935. First edition. 128 pages, 14 diagrams. 75 cents. (*Tomorrow, Publishers, New York.*)

This book is of interest to the medical profession for its clear, authoritative and concise discussion of the genetical basis of heredity. There are excellent discussions of the present status of the theory of evolution and the nature of variations, and there is a clarification of the widely misused term "race." To cite only one of the book's many applications in medicine, it is valuable for its presentation of the state of contemporary knowledge regarding the heredity of mental deficiency in man, which bears on the question of whether or not sterilization of the mentally deficient would be of advantage to society as a whole. The author's conclusions on this question may be epitomized by the following:

". . . a great deal of genetic research has yet to be done before we ascertain the real genetic nature of the detrimental characters of men. We must not permit the unscientific blabber about the Jukes and Kallikaks to influence us to believe that human genetics can be studied by means of the gossip employed in those tales. It should be obvious that we cannot say anything about human genetics until we control the environment as a variable. Unless we control the environment so as to give each child the best our civilization, our inventiveness and our progress have to offer, we cannot say much about its real genetic make-up. . . .

". . . Most of the harmful characters in man, that is, the few that have been studied, are recessive. It can be shown mathematically that in any population

in which some recessive gene is present, the vast majority of individuals showing the recessive character will come from normal parents that are heterozygous for the recessive. About ninety per cent of all genetically feeble-minded individuals come from normal parents, each of whom carried the gene for feeble-mindedness in the recessive state. It has been calculated that if every feeble-minded person were sterilized, the number of feeble-minded would be reduced to one-half in two thousand years. Obviously, under present conditions, favoring sterilization is not worth the risk" . . . of its unscrupulous use.

E. H.

Physiology in Modern Medicine. By J. J. R. MACLEOD. 1935. Seventh edition. 1154 pages, 297 illustrations. $8.50. (*C. V. Mosby and Co., St. Louis, Mo.*)

This new edition of one of the standard texts of physiology is to a considerable extent a collective effort. Seven out of the ten parts of the book have been partly or wholly revised or rewritten by collaborators of the original author. In the present edition Dr. Macleod has been ably assisted by Philip Bard, Edward P. Carter, J. M. D. Olmsted, J. M. Peterson and N. B. Taylor. The authorship of the book is in itself evidence of the fact that physiology, like other sciences, is ceasing to be a craft which can be carried on by an isolated individual, and is becoming, not exactly a mass-production industry, but more and more clearly a social product involving group activity.

The book is admirable as a source of reference to current physiological concepts. However, it has a somewhat unavoidably diffuse quality, which makes one long for the day when physiology will have approached more closely to an exact science and be more amenable to precise generalizations.

E. H.